NCCN National Comprehensive Cancer Network®

NCCN

Senior Adult Oncology, Version 2.2014

Clinical Practice Guidelines in Oncology

Arti Hurria, MD; Tanya Wildes, MD; Sarah L. Blair, MD; Ilene S. Browner, MD; Harvey Jay Cohen, MD; Mollie deShazo, MD; Efrat Dotan, MD; Barish H. Edil, MD; Martine Extermann, MD, PhD; Apar Kishor P. Ganti, MD; Holly M. Holmes, MD; Reshma Jagsi, MD, PhD; Mohana B. Karlekar, MD; Nancy L. Keating, MD, MPH; Beatriz Korc-Grodzicki, MD, PhD; June M. McKoy, MD, JD, MBA; Bruno C. Medeiros, MD; Ewa Mrozek, MD; Tracey O'Connor, MD; Hope S. Rugo, MD; Randall W. Rupper, MD, MPH; Rebecca A. Silliman, MD, PhD, MPH; Derek L. Stirewalt, MD; William P. Tew, MD; Louise C. Walter, MD; Alva B. Weir, III, MD; Mary Anne Bergman; and Hema Sundar, PhD

Overview

Cancer is the leading cause of death in women and men aged 60 to 79 years.[1] More than 50% of all cancers and more than 70% of cancer-related deaths in the United States occur in patients who are 65 years or older.[2] Experts estimate that by 2030 approximately 70% of all cancers will be diagnosed in adults aged 65 years or older.[3] Older adults are more prone to develop cancer than younger adults. Furthermore,

Abstract

Cancer is the leading cause of death in older adults aged 60 to 79 years. The biology of certain cancers and responsiveness to therapy changes with the patient's age. Advanced age alone should not preclude the use of effective treatment that could improve quality of life or extend meaningful survival. The challenge of managing older patients with cancer is to assess whether the expected benefits of treatment are superior to the risk in a population with decreased life expectancy and decreased tolerance to stress. These guidelines provide an approach to decision-making in older cancer patients based on comprehensive geriatric assessment and also include diseasespecific issues related to age in the management of some cancer types in older adults. (*J Natl Compr Canc Netw* 2014;12:82–126)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Senior Adult Oncology are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Senior Adult Oncology Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Senior Adult Oncology Panel members can be found on page 126. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

aging in the US population and increased life expectancy mean that cancer in older adults is becoming an increasingly common problem.

Caring for an older adult with cancer involves unique issues. The biology of certain neoplasms and responsiveness to therapy changes with the patient's age.[4] Furthermore, the patient's physiologic status, comorbidities, and preferences may influence the selection and tolerance to certain therapies. Together, these age-related issues form the basis for the development of guidelines that address special considerations in older patients with cancer.

Older patients with cancer are underrepresented in clinical trials for new cancer therapies.[5] Therefore, fewer evidence-based data are available to guide the treatment of these patients. However, advanced age alone should not preclude the use of effective cancer treatment that could improve quality of life or extend meaningful survival.[6,7] Treatment that diminishes quality of life with no significant survival benefit should be avoided. The available data suggest that older patients with good performance status are able to tolerate commonly used chemotherapy regimens as well as younger patients, particularly when adequate supportive care is provided.[8–10] However, few studies have addressed patients at the extremes of age or those with poor performance status. The physiologic changes associated with aging may impact an older adult's ability to tolerate cancer therapy and should be considered in the treatment decision-making process.

Proper selection of patients is the key to administering effective and safe cancer treatment. The

Text cont. on page 100.

NCCN Senior Adult Oncology Panel Members

*Arti Hurria, MD/Chair†Þ
City of Hope Comprehensive Cancer Center
*,[b]Tanya Wildes, MD/Vice-Chair†‡
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
Sarah L. Blair, MD¶
UC San Diego Moores Cancer Center
[c,h]Ilene S. Browner, MD†
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
[h]Harvey Jay Cohen, MD†
Duke Cancer Institute
[d]Mollie deShazo, MD†
University of Alabama at Birmingham Comprehensive Cancer Center
[c]Efrat Dotan, MD†
Fox Chase Cancer Center
Barish H. Edil, MD¶
University of Colorado Cancer Center
*,[h]Martine Extermann, MD, PhD†
Moffitt Cancer Center
[e]Apar Kishor P. Ganti, MD†
UNMC Eppley Cancer Center at The Nebraska Medical Center
[h]Holly M. Holmes, MDÞΣ
The University of Texas MD Anderson Cancer Center
Reshma Jagsi, MD, PhD§
University of Michigan Comprehensive Cancer Center
[g]Mohana B. Karlekar, MDÞ£
Vanderbilt-Ingram Cancer Center
*,[h]Nancy L. Keating, MD, MPHÞ
Dana-Farber/Brigham and Women's Cancer Center
[h]Beatriz Korc-Grodzicki, MD, PhD
Memorial Sloan-Kettering Cancer Center
[h]June M. McKoy, MD, JD, MBA
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
*,[b]Bruno C. Medeiros, MD‡
Stanford Cancer Institute
[a]Ewa Mrozek, MD†‡
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute
[a]Tracey O'Connor, MD†
Roswell Park Cancer Institute
[a]Hope S. Rugo, MD†‡
UCSF Helen Diller Family Comprehensive Cancer Center
[h]Randall W. Rupper, MD, MPH
Huntsman Cancer Institute at the University of Utah
*,[h]Rebecca A. Silliman, MD, PhD, MPH
Boston University Medical Center
*,[b]Derek L. Stirewalt, MD†
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
[a]William P. Tew, MD†Þ
Memorial Sloan-Kettering Cancer Center
[h]Louise C. Walter, MD
UCSF Helen Diller Family Comprehensive Cancer Center
[f]Alva B. Weir, III, MD†‡
St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center

NCCN Staff: Mary Anne Bergman and Hema Sundar, PhD

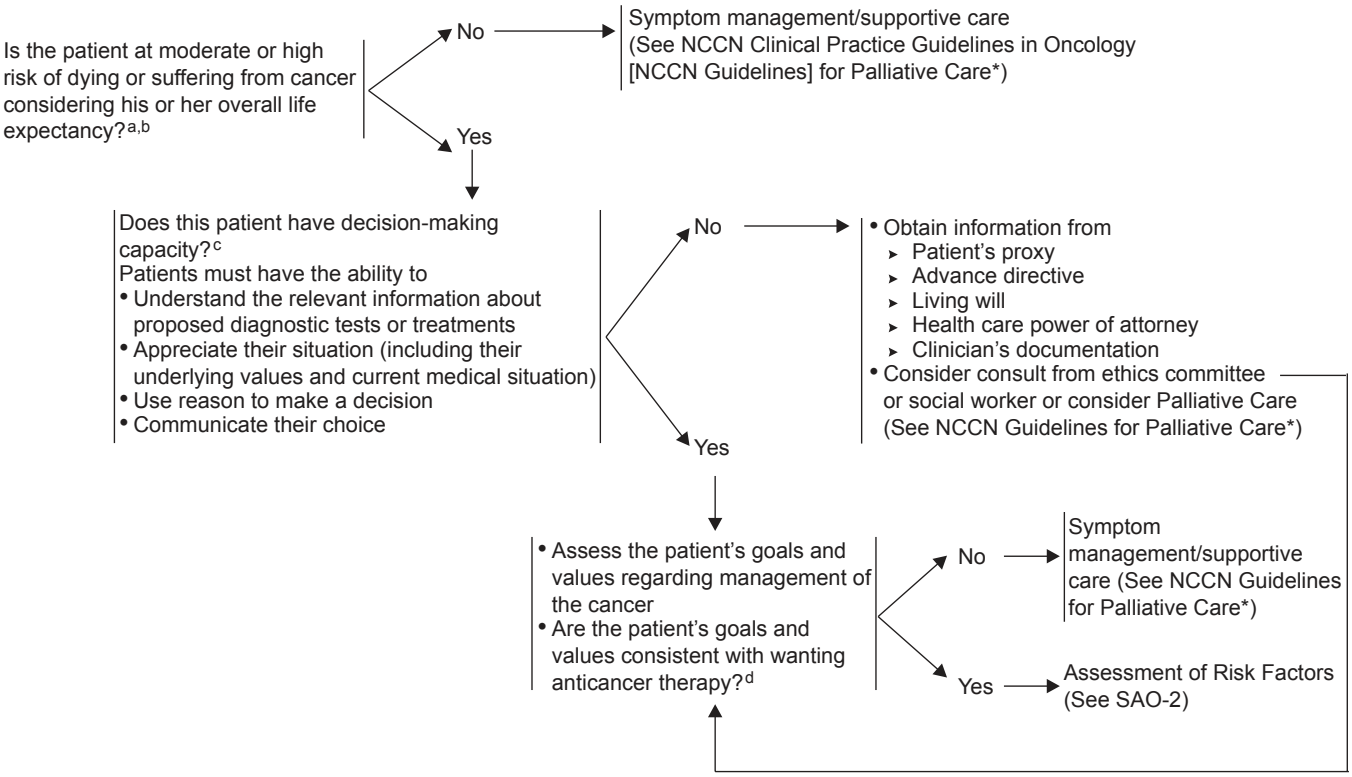
KEY:

*Writing Committee Member

Subcommittees: [a]Breast/Gynecologic Cancers; [b]Hematologic Malignancies; [c]Gastrointestinal Cancers; [d]Bladder, Kidney, and Prostate Cancers; [e]Non–Small Cell Lung Cancers; [f]Head and Neck Cancers/Central Nervous System Cancers; [g]Psychosocial/ Palliative Care; [h]Geriatric Assessment

Specialties: ¶Surgery/Surgical Oncology; †Medical Oncology; ‡Hematology Oncology; §Radiation Oncology; Geriatric Medicine; ÞInternal Medicine, Including Family Practice and Preventive Management; £Supportive Care, Including Palliative and Pain Management

APPROACH TO DECISION-MAKING IN THE OLDER ADULT



*To view the most recent version of these guidelines, visit NCCN.org.

[a] Life expectancy calculators are available at www.eprognosis.com. Note that these calculators are used to determine anticipated life expectancy (independent of the cancer). They could be utilized in clinical decision-making to weigh whether the cancer is likely to shorten the patient's life expectancy or whether the patient is likely to become symptomatic from cancer during his or her anticipated life expectancy. Note that these calculators should be used in conjunction with clinical judgement.

[b] See histograms for age-specific life expectancy (SAO-A).

[c] Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? JAMA. 2011;306:420-427. (http://www.ncbi.nlm.nih.gov/pubmed/21791691). Copyright © (2012) American Medical Association. All rights reserved.

[d] Harrington SE, Smith TJ. The role of chemotherapy at the end of life: when is enough, enough? JAMA 2008;299:2667-2678.

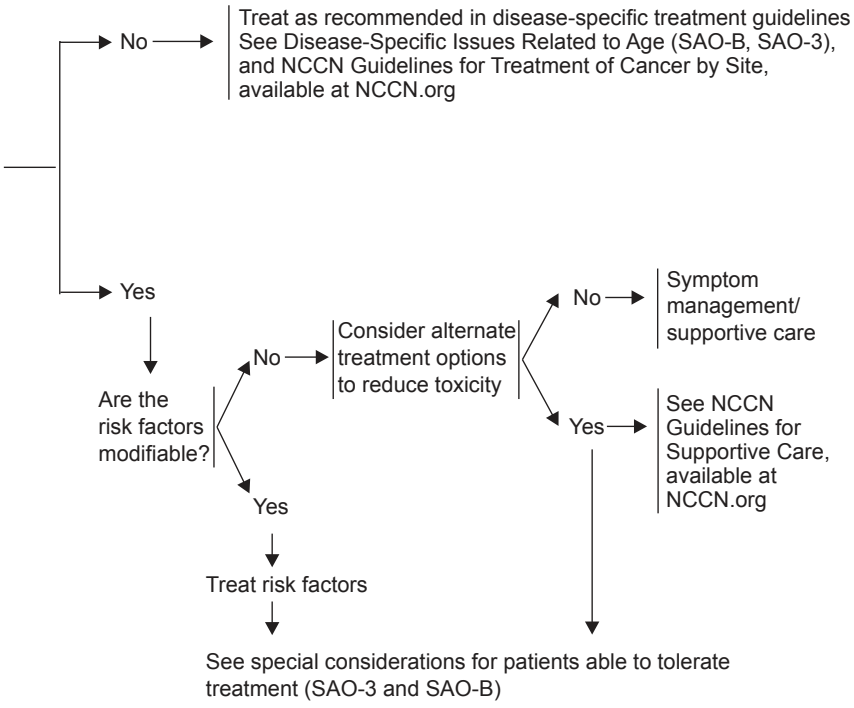
SAO-1

Senior Adult Oncology, Version 2.2014

ASSESSMENT OF RISK FACTORS[e]

Does the patient have risk factors for adverse outcomes from cancer treatment?

- Comorbidities[e]
  - cardiovascular disease[f]
  - renal insufficiency[g]
  - neuropathy
  - anemia
  - osteoporosis
    - See NCCN Bone Health Task Force (available at JCCN.org)
  - GI problems
  - diabetes
  - lung disease
  - hearing or vision loss
  - prior cancer diagnosis and treatment
  - chronic infections
  - decubitus or pressure ulcers
- Geriatric syndromes[e]
  - functional dependency (ADL, IADL)
  - mobility problems
  - falls
  - dementia
  - delirium
  - depression
  - nutritional deficiency
  - polypharmacy
- Socioeconomic issues
  - poor living conditions
  - no caregiver or limited social support
  - low income
  - transportation barriers/access problems
  - under-insurance and/or high out-of-pocket costs for medications



[e]See Comprehensive Geriatric Assessment (SAO-C).
[f]Older age has been associated with increased risk for congestive heart failure (CHF) in patients receiving cytotoxic and targeted therapies.
[g]The panel recommends calculation of creatinine clearance to assess renal function for all patients.

SPECIAL CONSIDERATIONS FOR PATIENTS ABLE TO TOLERATE TREATMENT[h,i]

Surgery

- In general, age is not the primary consideration for surgical risk.
- Emergency surgery carries increased risk of complications.
- Assess physiologic status.
- American Geriatrics Society (AGS) Task Force and American College of Surgeons provided general guidelines for older adults undergoing surgery.[1] These guidelines can be applied to older patients with cancer undergoing surgery.
- Data suggest that an increased need for functional assistance presurgery (measured by ADL, IADL, and PS) predicts postoperative complications, extended hospital stay, and 6-month mortality in older patients undergoing cancer surgery.[2-4]
- Impaired cognitive status is a risk factor for postoperative complications, prolonged length of stay, and 6-month overall mortality postoperatively.[2,5]
- In patients undergoing general surgery:
  - Older age is a risk factor for postoperative delirium.[6]
  - Delirium is a risk factor for functional decline.[7] See Assessment of Cognition (SAO-E).
- Preventive measures exist for delirium
  - Yale Delirium Prevention Trial and Hospitalized Elder Life Program (HELP): http://info.med.yale.edu/intmed/elp/print_version/background_print.htm
  - National Institute for Health and Clinical Excellence (NICE) Guideline for Prevention of Delirium: http://publications.nice.org.uk/delirium-cg103

Radiation Therapy

- Use caution with concurrent chemoradiation therapy; dose modification of chemotherapy may be necessary.
- Nutritional support and pain control are needed if radiation therapy-induced mucositis is present.

Systemic Therapy

- Chemotherapy toxicity risk can be predicted by parameters that are typically included in a Comprehensive Geriatric Assessment (CGA). These tools are awaiting additional validation.
  - Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score (http://eforms.moffitt.org/crashScore.aspx)
  - Cancer and Aging Research Group (CARG) Chemo Toxicity Calculator (http://www.mycarg.org)

Systemic Therapy Continued on SAO-4

[h] Monitor the patient's functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
[i] See Disease-specific issues related to age (SAO-B).

[1] Chow WB, Rosenthal RA, Merkow RP, et al. Optimal pre-operative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg 2012;215:453-466.
[2] Fukuse T, Satoda N, Hijiya K, et al. Importance of a comprehensive geriatric assessment in prediction of complications following thoracic surgery in elderly patients. Chest 2005;127:886-891.
[3] Audisio RA, Pope D, Ramesh HS, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008;65:156-163.
[4] Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg 2009;250:449-455.
[5] Robinson TN, Wu DS, Pointer LF, et al. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg 2012;215:12-17; discussion 17-18.
[6] Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective non-cardiac surgery. JAMA 1994;271:134-139.
[7] Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc 2010;58:643-649.

SPECIAL CONSIDERATIONS FOR PATIENTS ABLE TO TOLERATE TREATMENT[h,i]

Systemic Therapy

Diarrhea	• Consider early aggressive rehydration • Manage with octreotide if oral preparations are ineffective (see NCCN Guidelines for Palliative Care*)
Constipation	• See NCCN Guidelines for Palliative Care*
Nausea/vomiting	• See NCCN Guidelines for Antiemesis* and NCCN Guidelines for Palliative Care*
Mucositis	• Early hospitalization is needed for patients who develop dysphagia/diarrhea • Provide nutritional support • See NCCN Task Force: Prevention and Management of Mucositis in Cancer Care, available at JNCCN.org
Bone marrow suppression	• Prophylactic colony-stimulating factors are needed when dose intensity is required for response or cure (See NCCN Guidelines for Myeloid Growth Factors*)
Neurotoxicity	• Consider alternative regimens with non-neurotoxic drugs • Monitor hearing loss and avoid neurotoxic agents if significant hearing loss is present • Monitor cerebellar function if high-dose cytarabine is present • Monitor for peripheral neuropathy
Falls	• Assessment of history of falls, balance, and gait difficulties is recommended for all patients.[e,j]
Cardiac toxicity	• Monitor for symptomatic or asymptomatic congestive heart failure (CHF) ▸ Caution with use of anthracyclines; consider alternative treatment ▸ Caution with use of trastuzumab[k,l] (among patients with a normal ejection fraction, risk factors for CHF include receipt of an anthracycline-based regimen, baseline LVEF of 50%-54%, and hypertensive medicines)
Renal toxicity	• Calculate creatinine clearance to assess renal function • Adjust dose for glomerular filtration rate to reduce systemic toxicity
Insomnia[m]	• Benzodiazepines or other sedative-hypnotics should not be used as first-line treatment for insomnia in older adults.[n] • Nonpharmacologic methods, such as cognitive behavioral therapy and lifestyle modifications, are preferred.

*To view the most recent version of these guidelines, visit NCCN.org.

[e] See Comprehensive Geriatric Assessment (SAO-C).
[h] Monitor the patient's functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
[i] See Disease-specific issues related to age (SAO-B).
[j] Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med 2003;348:42-49.
[k] Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-1672.
[l] Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-1684.
[m] See Insomnia (SAO-G).
[n] American Geriatrics Society: Five Things Physicians and Patients Should Question (http://www.choosingwisely.org/doctor-patient-lists/american-geriatrics-society/).

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Acute Lymphoblastic Leukemia†

See NCCN Guidelines for Acute Lymphoblastic Leukemia*

It is strongly recommended that older adults with acute lymphoblastic leukemia (ALL) be treated in a specialized center.

Philadelphia Chromosome-Positive ALL

- A randomized study of patients older than 55 years with Philadelphia chromosome-positive ALL (Ph+ALL) compared imatinib with chemotherapy as front-line treatment. The study demonstrated that imatinib is well tolerated with a higher remission rate and comparable overall survival (OS) in comparison to chemotherapy alone.[1]
- Phase II studies of adults with Ph+ALL treated with a tyrosine kinase inhibitor (imatinib or dasatinib) with steroids and intrathecal chemotherapy demonstrated a high response rate (100% with complete hematologic remission) and no early deaths.[2,3]
- A phase II study of patients aged 55 years and older with Ph+ALL of induction chemotherapy followed by imatinib with steroids demonstrated higher complete response (CR) rate and survival than historical studies of chemotherapy alone.[4]

Other ALL Studies

- Hyper CVAD in older patients with ALL results in higher CR rates and OS (compared with historical regimens); however, there is a higher risk of myelosuppression-related deaths. Of note, the dose of Ara-C was reduced to 1 g/m^2 in patients older than 60 years.[5]
- A randomized phase II study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in patients older than 55 years with ALL demonstrated no benefit to pegylated liposomal doxorubicin versus continuous-infusion doxorubicin.[6]
- The benefit of adding rituximab to chemotherapy in older adults with Ph(-) CD20+ ALL has not been demonstrated.[7]

*To view the most recent version of these guidelines, visit NCCN.org.

[1] Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph1ALL). Cancer 2007;109:2068–2076.
[2] Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521-6528.
[3] Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-3678.
[4] Delannoy A, Delabesse E, Lheritier V, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. Leukemia 2006;20:1526–1532.
[5] O'Brien S, Thomas DA, Ravandi F, et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. Cancer 2008;113:2097–2101.
[6] Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. Haematologica 2011;96:245-252.
[7] Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome–negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol 2010;28:3880-3889.
† For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Acute Myeloid Leukemia

See NCCN Guidelines for Acute Myeloid Leukemia*

- Increasing age is a poor prognostic indicator in older adults with acute myeloid leukemia (AML). Other poor prognostic indicators are: FLT3 internal tandem duplications, unfavorable cytogenetics, increasing white blood cell count, poorer PS, and presence of secondary AML. Prediction tools are available to assist in counseling older adults regarding the safety and efficacy of standard induction chemotherapy.[1-4]
- A randomized phase II trial of patients older than 55 years receiving induction chemotherapy for AML with Ara-C (100 mg/m^2/d IV for 7 days) demonstrated no difference in efficacy with the addition of the following anthracycline-containing regimens: daunorubicin, 45 mg/m^2/d IV on days 1-3; mitoxantrone, 12 mg/m^2/d on days 1-3; and idarubicin, 12 mg/m^2/d on days 1-3.[5]
- A randomized phase III trial of patients older than 56 years with previously untreated AML demonstrated no difference in CR rate between AD (Ara-C, 200 mg/m^2/d IV continuous infusion on days 1-7 and daunorubicin, 45 mg/m^2/d on days 1-3) and ME (mitoxantrone, 10 mg/m^2/d IV on days 1-5 and etoposide, 100 mg/m^2/d IV on days 1-5); however, poorer OS at 2 years was seen in the ME arm. Therefore, if standard induction chemotherapy (off protocol) is given, an Ara-C-containing regimen should be used.[6]
- A randomized phase II trial of patients older than 60 years with Ara-C (100 mg/m^2/d IV for 7 days) demonstrated that higher doses of daunorubicin (90 vs 45 mg/m^2 given IV over 3 h days 1-3) was associated with a superior CR rate but no difference in OS; however, a post hoc analysis showed a potential benefit to the higher dose of daunorubicin in patients older than 65 years, especially in those with CBF-AML.[7]
- Standard-induction chemotherapy is associated with a 10% to 20% risk of death in patients older than 56 years. The risk of obtaining a CR and the risk of treatment-related mortality (taking age into account) can be calculated using a Web-based tool[8] (http://www.aml-score.org/).

*To view the most recent version of these guidelines, visit NCCN.org.

[1] Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302-1311.
[2] Burnett AK, Milligan D, Goldstone A, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. Br J Haemato 2009;145:318-332.
[3] Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. Br J Haematol 2009;145:598-605.
[4] Stirewalt DL, Kopecky KJ, Meshinchi S, et al. Size of FLT3 internal tandem duplication has prognostic significance in patients with acute myeloid leukemia. Blood 2006;107:3724-3726.
[5] Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 2004;103:479-485.
[6] Anderson JE, Kopecky KJ, Willman CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood 2002;100:3869-3876.
[7] Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235-1248.
[8] Krug U, Röllig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 2010;376:2000-2008.

Multiple Myeloma†

DISEASE-SPECIFIC ISSUES RELATED TO AGE

See NCCN Guidelines for Multiple Myeloma*

Initial Therapy:

- Choice of treatment depends on the side effect profile but also the ability to travel for IV therapy. Initial evaluation should determine whether the patient is potentially a candidate for high-dose therapy and autologous stem cell transplantation, because melphalan should be avoided in transplant candidates. There is a lack of consensus on what constitutes transplant eligibility; determining whether a patient is eligible for transplant incorporates assessment of physiologic age rather than chronologic age, with attention to comorbidities, functional status, and adequate cardiac, pulmonary, renal, and hepatic function. Consider early referral to a transplant physician if uncertain whether the patient is transplant-eligible before exposure to alkylating agents. For more information regarding transplant eligibility, go to http://www.cms.gov/.

Immunomodulator-Based Initial Therapy:

- Older adults with multiple myeloma receiving MPT (melphalan, prednisone, and thalidomide) in comparison to MP (melphalan and prednisone) had a higher response rate at the cost of increased toxicity (constipation, fatigue, increased venous thromboembolism [VTE], neuropathy, cytopenias, and infection).[1-9]
- A survival benefit has been seen with MPT compared with MP, although studies are conflicting and varying doses of thalidomide have been used.[1-9]
- MPT is associated with higher response rate and OS than transplant with intermediate-dose melphalan (MEL 100).[2]
- Melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged PFS in patients 65 years or older with newly diagnosed multiple myeloma who were ineligible for transplantation. The greatest PFS benefit was observed in patients 65 to 75 years of age.[10]

VTE Prophylaxis:

- In elderly patients receiving immunomodulator-based regimen, VTE prophylaxis is recommended.[11]

Bortezomib-Based Initial Therapy:

- VMP (bortezomib, melphalan, and prednisone) in comparison to MP is associated with an increased response rate and OS at the cost of increased toxicity (eg, peripheral neuropathy, cytopenias, fatigue). The survival benefit is maintained across age groups.[12,13]
- VMP versus VTP (bortezomib, thalidomide, and prednisone) have similar response rates and OS but differing side effect profiles (VMP [ie, hematologic toxicity, infection] and VTP [cardiac complications]). Rates of neuropathy were similar in both groups.[14]
- VMPT (bortezomib, melphalan, prednisone, and thalidomide) followed by maintenance VT (bortezomib and thalidomide) versus VMP is associated with a higher response rate but does not improve OS. Weekly bortezomib is associated with a decreased rate of peripheral neuropathy without a decrement in response.[15] An updated analysis (with a median follow-up of 47.2 months) showed that VMPT-VT regimen significantly prolonged OS compared with VMP, especially in patients younger than 75 years.[16]

High-Dose Dexamethasone Is Excessively Toxic in Older Adults:

- High-dose dexamethasone is associated with an increased risk of mortality and severe hematologic toxicities compared with MP.[17]
- Lenalidomide plus low-dose dexamethasone (in comparison to lenalidomide plus high-dose dexamethasone) is associated with an improvement in OS and lower toxicity (less DVT and fatigue and fewer infections).[18]

[1] Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16-22.
[2] Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209-1218.
[3] Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664-3670.
[4] Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant-ineligible patients with multiple myeloma: a meta-analysis. Leukemia 2011;25:1523-1524.
[5] Ludwig H, Hajek R, Tothova E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009;113:3435-3442.
[6] Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825-831.
[7] Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 2008;112:3107-3114.
[8] Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405-1412.
[9] Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28:3160-3166.
[10] Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759-1769.
[11] Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011;29:986-993.
[12] Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259-2266.
[13] San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-917.
[14] Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010;11:934-941.
[15] Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101-5109.
[16] Palumbo A, Bringhen S, Rossi D, et al. Overall survival benefit for bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients [abstract]. Blood 2012;120: Abstract 200.
[17] Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 2006;107:1292-1298.
[18] Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37.

†For Comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Myelodysplastic Syndromes

See NCCN Guidelines for Myelodysplastic Syndromes*

- Azacytidine is the standard of care in patients with higher-risk MDS with improvement in OS, time to AML transformation, and quality of life, as well as decreased transfusion dependence. Subgroup analysis demonstrated similar benefits, with no increased risk of toxicity in patients 65 years of age and older and those 75 years of age and older. Predictors of a better response include a bone marrow blast count less than 15%, a normal karyotype, and no previous treatment with low-dose cytosine arabinoside.[1-3]
- The standard of care for patients with higher-risk MDS is azacytidine given 7 days in a row; however, this may be challenging due to logistic or transportation problems. A phase II study evaluating patients 65 years of age and older showed that the 5+2+2 (5 days on, 2 days off, 2 days on) schedule did not seem to negatively impact the response rate or duration of response. A 5-day schedule is not recommended for these patients.[1,4]
- Two large studies have evaluated the 5-day decitabine regimen for treatment of lower- and higher-risk MDS patients, in a predominantly elderly patient population.[5,6] Substantial responses and hematologic improvements were demonstrated, with median survivals of 20 months in both studies. These results are comparable to those reported with azacytidine.
- Among patients with higher-risk MDS, decitabine delivered on an inpatient schedule over 3 days is not associated with a survival advantage in comparison to best supportive care.[7]
- Lenalidomide can reduce red blood cell (RBC) transfusion requirements in patients with lower-risk MDS with the 5q31 deletion.[8] It can also reverse cytologic and cytogenetic abnormalities in these patients. The drug may reduce RBC transfusion requirements in a subset of other lower-risk MDS patients.[9] Although the median age of patients included in these studies is early 70s, few data are available regarding the risks and benefits at the extremes of age.[8,9]
- Older age is associated with a lower chance of response to immunosuppression strategies (cyclosporine or antithymocyte globulin [ATG] +/- cyclosporine) in patients with low-risk MDS.[10]

*To view the most recent version of these guidelines, visit NCCN.org.

[1] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223-232.
[2] Seymour JF, Fenaux P, Silverman LR, et al. Effects of azacitidine compared with conventional care regimens in elderly (≥75 years) patients with higher-risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2010;76:218-227.
[3] Itzykson R, Thepot S, Quesnel B, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood 2011;117:403-411.
[4] Breccia M, Loglisci G, Salaroli A, et al. 5-azacitidine efficacy and safety in patients aged >65 years with myelodysplastic syndromes outside clinical trials. Leuk Lymphoma 2012;53:1558-1560.
[5] Kantarjian HM, O'Brien S, Shan J, et al. Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome. Cancer 2007;109:265-273.
[6] Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol 2009;27:3842-3848.
[7] Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011;29:1987-1996.
[8] List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-1465.
[9] Raza A, Reeves JE, Feldman EJ, et al. Phase II study of lenalidomide in transfusion-dependent, low and intermediate-1-risk myelodysplastic syndromes with normal and abnormal karyotypes other than deletion 5q. Blood 2008;111:86-93.
[10] Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol 2008;26:2505-2511.

COMPREHENSIVE GERIATRIC ASSESSMENT

Functional status[i]
- Activities of Daily Living (ADL) - Eating, dressing, continence, grooming, transferring, using the bathroom
- Instrumental Activities of Daily Living (IADL) - Using transportation, managing money, taking medications, shopping, preparing meals, doing laundry, doing housework, using the telephone
- Performance status
- Falls
  - In patients who have experienced a fall in the last 6 months or if the patient is "afraid of falling," consider the following evaluations:
    - Assessment of gait using Timed Up and Go (TUG) test: See SAO-D
    - PT or OT evaluation
    - Checking and replacing vitamin D levels
    - Referral to geriatrics or primary care physician
- Gait speed[1]

Socioeconomic issues: See SAO-2
Psychosocial distress: See NCCN Guidelines for Distress Management*

Comorbidities
- May affect treatment decisions in 5 ways:
  - Comorbidity may modify cancer behavior.
  - Cancer treatment may interact with comorbidity to impact functional status or worsen comorbidity. This includes any drug-drug interactions.
  - Cancer treatment may be too risky because of the type and severity of comorbidity.
  - Comorbidity may influence life expectancy (independent of the cancer).
  - Comorbidity may affect treatment outcome.

Cognitive function (See Assessment of Cognitive Function, SAO-E)
- Dementia
  - Mini-Mental State Examination (MMSE)[2,3]
  - Montreal Cognitive Assessment (MoCA)[4] (http://www.mocatest.org/)
- Depression
  - Geriatric Depression Scale (GDS)[5,6]
  - See NCCN Guidelines for Distress Management*
- Delirium
  - Confusion Assessment Method and/or Memorial Delirium Assessment Scale[7,8]
  - See NCCN Guidelines for Palliative Care* and NCCN Guidelines for Distress Management*

*To view the most recent version of these guidelines, visit NCCN.org.

[i] See Procedure for Functional Assessment Screening in Elderly Persons (SAO-H).

COMPREHENSIVE GERIATRIC ASSESSMENT

Polypharmacy

- Medication review (prescription and over-the-counter medications, vitamins, and supplements) for duplication and appropriate use should be performed at every visit and evaluated for potentially inappropriate medication use.
  - Medication Appropriateness Index[9]
  - Beers Criteria[10]
  - STOPP/START Criteria[11,12]
- Review drug interactions and drug-supplement interactions[13]
  - http://medicine.iupui.edu/clinpharm/ddis/
  - http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products
- Carefully review indications, duration of therapy, and dosage when using these medications or classes of medications[14,15]

  - Benzodiazepines
  - Anticholinergics
  - Antipsychotics
  - Opioids
  - Corticosteroids
  - Antihistamines
  - Oxybutynin
  - Sleep medications
  - Neuroleptics
  - Antidepressants
  - Anticonvulsants
  - Class 1A antiarrhythmics
- Evaluate adherence to therapy (See Assessment of Adherence, SAO-F)

Nutritional status

- Body mass index
- Weight loss
- Nutritional deficiency - Mini Nutritional Assessment (MNA)[16,17]

REFERENCES

[1] Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50-58.
[2] Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc1992;40:922-935.
[3] Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386-2391.
[4] Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
[5] Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.
[6] D'Ath P, Katona P, Mullan E, et al. Screening, detection and management of depression in elderly primary care attenders: the acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994;11:260-266.
[7] Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-948.
[8] Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: Assessing delirium in advanced cancer. Cancer 2000;88:2859-2867.
[9] Samsa GP, Hanlon JT, Schmader KE, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol 1994;47:891-896.
[10] American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616-631.
[11] Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment) – an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007;36:632-638.
[12] Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673-679.
[13] Riechelmann RP, Saad ED. A systemic review on drug interactions in oncology. Cancer Invest 2006;24:704-712.
[14] Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med 2007;167:781-787.
[15] Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of the 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333-1341.
[16] Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition1999;15:116-122.
[17] Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the Short-Form Mini-Nutritional Assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366-372.

ASSESSMENT OF GAIT AND TREATMENT RECOMMENDATIONS

Gait should be assessed using the Timed Up and Go (TUG) test.[1]

- The TUG test is calculated as the time in seconds it takes a patient to stand up from a chair (without using his or her arms), walk 10 feet straight ahead, turn back, and return to the chair and sit down. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person.
- A normal TUG test score is less than 13 seconds. For patients with above-normal TUG test scores, consider comprehensive evaluation as indicated below.

ASSESSMENT	TREATMENT RECOMMENDATIONS
Assess proximal muscle strength	• Diagnose and treat underlying causes • Consider physical therapy evaluation
Check orthostatic blood pressure	• Diagnose and treat underlying causes • Review medications • Address salt intake, adequate hydration, and compensatory strategies (eg, elevating head of bed, rising slowly, using pressure stockings)
Ask about changes in vision	• Diagnose and treat underlying cause of vision changes • Consider referral to opthalmologist • Consider neurologic evaluation
Assess for neurologic changes	• Evaluate if cancer or cancer treatment-related and modify treatment if possible • Consider neurologic evaluation
Review medications	• See “Polypharmacy” (SAO-C, 2 of 2) • Minimize the use of high-risk medications such as: benzodiazepines, sleeping medications, neuroleptics, antidepressants, anticonvulsants, or class 1A antiarrhythmics
Environmental hazards	• Consider home safety evaluation • Educate patients to reduce risk (http://www.cdc.gov/HomeandRecreationalSafety/Falls/CheckListForSafety.html)
Footwear assessment	• Assess type, condition, and fit of shoes • Perform foot exam

[1] Pondal M, del Ser T. Normative data and determinants for the timed "up and go" test in a population-based sample of elderly individuals without gait disturbances. [Research Support, Non-U.S. Gov't]. J Geriatr Phys Ther 2008;31(2):57-63.

ASSESSMENT OF COGNITIVE FUNCTION[1]

WHEN TO ASSESS FOR COGNITIVE FUNCTION	RECOMMENDATIONS
Would impaired cognitive function affect the planning or delivery of care? (eg, impact life expectancy or risk/benefit, impact adherence to treatment plan)	No (to all) → Reassess periodically or when considering treatment plan changes
Is the medical team concerned about decision-making capacity? See SAO-1	Yes (to any) → Consult with a clinician experienced in cognitive evaluation (ie, geriatrician, neurologist, geriatric psychiatrist, neuropsychologist) OR Initiate the evaluation yourself
Does the medical team suspect impaired cognitive function?	
Has the patient or patient's family suggested that the patient has impaired cognitive function?	

See SAO-E (2 of 2)

[1] Cordell CB, Borson S, Boustani M, et al. Medicare Detection of Cognitive Impairment Workgroup. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness visit in a primary care setting. Alzheimers Dement 2013;9:141-150.

ASSESSMENT OF COGNITIVE FUNCTION[1]

	Mild Cognitive Impairment	Dementia	Delirium
Definition	An intermediate state between normal cognition and dementia characterized by: • Subjective memory impairment • Preserved general cognitive function • Intact ability to perform daily functions	A progressive condition characterized by: • Impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function) • Interference with ability to perform daily functions	Disturbance of consciousness with: • Reduced ability to focus, sustain, or shift attention • Onset over a short period of time (usually hours to days) • Fluctuation during the course of the day
Distinguishing features	• Subjective memory complaints and awareness of memory changes • Preserved function	• Progressive (not sudden) loss of multiple cognitive abilities • Affects the ability to function independently	• Acute onset • Waxing and waning attention • Associated with physiologic disturbances
Differential Diagnosis (confounding factors)	CNS metastases Psychiatric disease (depression, anxiety, apathy) Endocrine dysfunction (thyroid) Metabolic causes (B12 deficiency) Drug dependency (including alcohol) Medication related Sleep disturbance Common geriatric conditions (pain, infection, constipation)		
Screening tool	Clinical interview with cognitive (Mini-Cog) and functional (ADL/IADL) assessment	Clinical interview with cognitive (Mini-Cog) and functional (ADL/IADL) assessment	Confusion Assessment Method (CAM)
Further evaluation	• Reassess periodically and with major changes in condition or when considering changes to treatment plan • Consider consultation with a clinician experienced in cognitive evaluation	• Consult with a clinician experienced in cognitive evaluation and treatment • Neuropsychological testing may be indicated • Evaluation: B12, TSH, brain imaging	• Evaluate and treat all potential causes of delirium • Consider consultation with clinicians experienced in cognitive evaluation and treatment

[1] Cordell CB, Borson S, Boustani M, et al. Medicare Detection of Cognitive Impairment Workgroup. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness visit in a primary care setting.

SAO-E (2 of 2)

ASSESSMENT OF ADHERENCE

Assess risk of nonadherence whenever considering a treatment regimen that will include an oral agent

Although older age per se is not a consistent risk factor for nonadherence, several factors may increase the potential for nonadherence among older adults:

- Deceased propensity of older adults to ask questions about benefits and risks of treatments
- Increased numbers of comorbidities and associated medications leading to regimen complexity
- Increased likelihood of side effects adversely affecting comorbidities
- Increased likelihood of prior experience with medication side effects
- Increased likelihood of drug-drug interactions
- Increased likelihood of acquisition barriers, including out-of-pocket costs, mobility/transportation difficulties, and lack of synchronized refill dates
- Increased risk of cognitive impairment

Strategies to minimize nonadherence

When initiating therapy:

- Ask patient to bring in prescribed, over-the-counter medications and supplements to review
- In collaboration with other medical providers, reduce regimen complexity, if possible
- Take into consideration cost of the medication including insurance coverage and out-of-pocket cost
- Consult with pharmacist to synchronize medication refills whenever possible[1]
- Prepare the patient regarding anticipated side effects to avoid inappropriate medication discontinuation
- Ensure that the patient/family understands the benefits/rationale for the medication and the risks of not taking it[2,3]
- Provide written instructions to patient/caregiver for taking the medication at the sixth grade level[4]. Have patient/caregiver repeat back his/her understanding of how to take the medication, common side effects, and "when to worry" and "what to do if worried"
- Engage family/other caregivers and interdisciplinary team in the process

At each follow-up visit:

- Ask patient to bring in prescribed, over-the-counter medications and supplements to review
- Provide additional cues or reminders (eg, calendars, pill boxes, other reminder techniques)
- Reinforce benefits and ask about side effects: if tolerable, stay the course; if intolerable, select an alternative
- Assess adherence in a nonjudgmental way: "How many pills did you take during the past week?" "How did you take them in relation to meals?" (if applicable)
- Ask the patient if there are any barriers to acquiring the medication; refer to case manager or pharmacist as applicable

[1] Agarwal S, et al. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? Am J Ther 2009;16(2):119-126.
[2] Steiner JF. Rethinking adherence. Ann Inter Med 2012;157:580-585.
[3] Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: A systematic review. Ann Intern Med 2012;157:785-795.
[4] Confirm ability to read and comprehend written instructions (eg, vision, literacy).

INSOMNIA

Insomnia →

The American Geriatrics Society (AGS) provides recommendations for the diagnosis, evaluation, and management of insomnia.

- Benzodiazepines or other sedative-hypnotics should not be used as first-line treatment for insomnia in older adults.[a]
- Nonpharmacologic methods such as cognitive behavioral therapy and lifestyle modifications are preferred.
- Patient should be cautioned that most over-the-counter sleep medications contain antihistamines and should not be used in older adults.
- If pharmacologic therapy is to be used, it is recommended for short-term use only with the lowest dose that is effective. The risks and benefits of the therapy should be discussed.[b] Please note that if zolpidem is considered, the FDA has advised that the recommended dose of zolpidem for women should be lowered from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products.[c]
- Patient information regarding optimizing sleep is available through the National Institute on Aging.[d]

[a] See American Geriatrics Society: Five Things Physicians and Patients Should Question (http://www.choosingwisely.org/doctor-patient-lists/american-geriatrics-society/).
[b] See AGS Geriatrics Evaluation and Management Tools (Geriatrics E&M Tools): http://www.americangeriatrics.org/files/documents/resources/GEMS/Insomnia.pdf
[c] See http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm.
[d] See http://www.nia.nih.gov/health/publication/good-nights-sleep.

SAO-G

PROCEDURE FOR FUNCTIONAL ASSESSMENT SCREENING IN ELDERLY PERSONS

Target Area	Assessment Procedure	Abnormal Result	Suggested Intervention
Vision	Test each eye with Jaeger card while patient wears corrective lenses (if applicable)	Inability to read >20/40	Refer to ophthalmologist
Hearing	Whisper a short, easily answered question, such as "What is your name?" in each ear while the examiner's face is out of direct view	Inability to answer question	Examine auditory canals for cerumen and clean if necessary. Repeat test; if still abnormal in either ear, refer for audiometry and possible prosthesis.
Arm	Proximal: "Touch the back of your head with both hands." Distal: "Pick up the spoon"	Inability to do task	Examine the arm fully (muscle, joint, and nerve) paying attention to pain, weakness, limited range of motion. Consider referral for physical therapy and occupational therapy.
Leg	Observe the patient after asking "Rise from your chair, walk 10 ft, return, and sit down"*	Inability to walk or transfer out of chair	Do full neurologic and musculoskeletal evaluation, paying attention to strength, pain, range of motion, balance, and traditional assessment of gait. Consider referral for physical therapy and occupational therapy.
Urinary incontinence	Ask patient: "Do you ever lose your urine and get wet?"	Yes	Ascertain frequency and amount. Search for remediable causes including local irritations, polyuric states, and medications. Consider urologic referral.
Nutrition	Weigh the patient; measure height	Weight is below acceptable range for height	Do appropriate medical evaluation. Consider dietician referral.
Mental status	Tell the patient: "I am going to name three objects (pencil, truck, book). I will ask you to repeat their names now and then again a few minutes from now"†	Inability to recall all 3 objects after 1 min	Administer Folstein mini-mental status examination. If score is < 24, search for causes of cognitive impairment. Ascertain onset, duration, and fluctuation of overt symptoms. Review medications. Assess consciousness and affect. Do appropriate laboratory tests.
Depression	Ask patient: "Do you often feel sad or depressed?"	Yes	Administer Geriatric Depression Scale. If positive (normal score, 0 to 10), check for antihypertensive, psychotropic, or other pertinent medications. Consider appropriate pharmaceutical or psychiatric treatment.
ADL-IADL	Ask patient: "Can you get out of bed yourself?"; "Can you dress yourself?"; "Can you make your own meals?"; "Can you do your own shopping?"	No to any question	Corroborate responses with patient's appearance; question family members if accuracy is uncertain. Determine reasons for the inability (motivation compared with physical limitation). Institute appropriate medical, social, or environmental interventions.
Home environment	Ask patient: "Do you have trouble with stairs inside or outside of your home?"; ask about potential hazards inside the home with bathtubs, rugs, or lighting	Yes	Evaluate home safety and institute appropriate countermeasures.
Social support	Ask patient: "Who would be able to help you in case of illness or emergency?"	…	List identified persons in the medical record. Become familiar with available resources for the elderly in the community. Consider social worker referral.

ADL, activities of daily living; IADL, instrumental activities of daily living.
Adapted with permission from Lachs MS, Feinstein AR, Cooney LM Jr, et al. A simple procedure for general screening for functional disability in elderly patients. Ann Intern Med 1990;112:699-706.
*This test is similar to the "Timed Up and Go" (TUG) test, except that the TUG test is calculated as the time in seconds it takes a patient to stand up from a chair (without using his or her arms), walk 10 feet straight ahead, turn back, and return to the chair and sit down. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person. A normal TUG test score is less than 13 seconds.
†This test is also referred to as the "three-item recall." It can be supplemented by the clock drawing test to assist in assessment for dementia.

SAO-H

Text cont. from page 83.

challenge of managing older patients with cancer is to assess whether the expected benefits of treatment are superior to the risk in a population with decreased life expectancy and decreased tolerance to stress. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Senior Adult Oncology address specific issues related to the management of cancer in older adults, including screening and comprehensive geriatric assessment (CGA), assessing the risks and benefits of treatment, preventing or decreasing complications from therapy, managing disease-specific issues, and managing patients deemed to be at high risk for toxicity from standard treatment.

CGA

Older patients can be classified into 3 categories: 1) young old patients are 65 to 75 years of age; 2) old patients are 76 to 85 years of age; and 3) oldest old patients are older than 85 years of age.[4] Chronologic age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications.[11] Although it is not possible for a physician to predict the exact life expectancy of an individual patient, providing an estimate of whether a patient is likely to live longer or shorter than an average person of similar age is possible.[12–17]

Life expectancy at a given age can be estimated using life table data as suggested by Walter and Covinsky.[12] For example, about 25% of the healthiest 75-year-old women will live more than 17 years, 50% will live at least 12 years, and 25% will live less than 7 years. Lee et al[14] developed and validated a potentially useful tool for clinicians to estimate the 4-year mortality risk. Patients can be stratified into 3 groups of varying risk of mortality (high, intermediate, or low) based on the prognostic index, which incorporates demographic variables (age and sex), self-reported comorbid conditions, and functional measures.[14] Carey et al[13] also developed a similar functional morbidity index based on self-reported functional status, age, and gender to stratify elders into varying risk groups for 2-year mortality.[13]

CGA is a multidisciplinary, in-depth evaluation to assess life expectancy and risk of morbidity and mortality in older patients.[18–20] CGA includes assessment tools to predict the functional age of older patients with cancer based on functional status, comorbidities that may interfere with cancer treatment, polypharmacy, nutritional status, cognitive function, psychological status, socioeconomic issues, and geriatric syndromes.

Functional Status

Functional status in older patients with cancer can be evaluated using self-reported or performance-based measures (see SAO-C 1 of 2, page 93). Self-reported measures include the individual's ability to complete activities of daily living (ADLs) and instrumental activities of daily living (IADLs).[21,22] ADLs encompass basic self-care skills required to maintain independence at home, and IADLs encompass complex skills that are necessary for maintaining independence in the community. The need for assistance with IADLs has been associated with decreased treatment tolerance and poorer survival in older patients with cancer.[23–26] Physical performance-based measures such as gait speed (also known as walking speed) and the Timed Up and Go (TUG) test are also used to assess functional status in older patients (see SAO-D, page 94).

Gait speed has been used to assess functional status and health outcomes in older adults.[17,27] Recent reports have also identified gait speed as an indicator of survival and mortality in older adults.[15,16] In a pooled analysis of individual data from 9 large cohort studies that included more than 30,000 participants (≥65 years) living in the community, Studenski et al[15] reported that gait speed was associated with survival in older adults. In this analysis, with 0.8 meter per second as the cutoff, gait speed faster than 1.0 meter per second suggested a better-than-average life expectancy and gait speed above 1.2 meters per second suggested exceptional life expectancy. White et al[16] reported that decline in gait speed (ranked as slow, moderate, and fast) could predict mortality in well-functioning older adults. A fast decline in gait speed was associated with a 90% greater risk of mortality than a slow decline.[16]

The predictive value of gait speed has also been evaluated in older patients with cancer.[28] In the Health, Ageing and Body Composition study that included 429 older patients with cancer, faster gait speed (time taken to cover a 20-meter course) was associated with lower risk of death (hazard ratio, 0.89) in patients with metastatic cancer and lower 2-year progression to death or disability in patients with nonmetastatic cancer.[28] Gait speed could be helpful in identifying older patients with a longer

expected life expectancy and who may be candidates for preventive interventions that are associated with long-term benefit.

The TUG test is a quick screening test to assess mobility and overall motor function in older adults.[29,30] The TUG test score is calculated as the time in seconds it takes a patient to get up from an armchair without using his or her arms, walk 10 feet forward at his or her usual pace, turn around, walk back to the chair, and then sit down again. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person. The TUG test score has been shown to predict the risk of falls in older adults.[31,32] In a preliminary prospective study, the TUG test was also associated with good sensitivity and specificity in the assessment of falls in older patients with cancer.[32]

Comorbidities

Older adults have an increased prevalence of comorbidities, which can impact cancer prognosis and treatment tolerance.[33,34] Cardiovascular problems including congestive heart failure (CHF), diabetes, renal insufficiency, dementia, depression, anemia, chronic infections, osteoporosis, decubitus or pressure ulcers, and prior cancer diagnosis and treatment are some of the frequently encountered comorbid conditions in older patients with cancer (see SAO-2, page 85).

Specific comorbidities have been shown to have an impact on prognosis and treatment outcome in patients with cancer.[35–37] For example, in a series of 5077 men (median age, 69.5 years) with localized or locally advanced prostate cancer, neoadjuvant hormonal therapy was significantly associated with an increased risk of all-cause mortality (26.3% vs 11.2%) among men with a history of coronary artery disease, CHF, or myocardial infarction after a median follow-up of 5.1 years.[35] In a randomized adjuvant chemotherapy trial of 3759 patients with high-risk stage II and stage III colon cancer, patients with diabetes mellitus experienced a significantly higher rate of overall mortality and cancer recurrence. At 5 years, the disease-free survival (DFS; 48% vs 59%), overall survival (OS; 57% vs 66%), and relapse-free survival (RFS; 56% vs 64%) rates were significantly worse for patients with diabetes compared with patients without diabetes.[36] In the SEER-Medicare database analysis of older patients (≥66 years) diagnosed with stages I to III breast cancer, those with diabetes had an increased rate of hospitalization for any chemotherapy toxicity and higher all-cause mortality.[37]

In older patients with cancer, comorbidity may modify the disease course (see SAO-C 1 of 2, page 92). The interaction of cancer treatment with comorbidity may impact functional status or worsen the comorbidity. Cancer treatment may be too risky due to the type and severity of comorbidity. Furthermore, comorbidity may influence life expectancy (independent of cancer). The effect of comorbidity on life expectancy should be evaluated before initiation of treatment.

The number and severity of comorbidities could be assessed with any of the following indices commonly used to determine the risk of mortality associated with comorbidity in older patients: adult comorbidity evaluation-27 (ACE-27) index,[38] the Charlson Comorbidity Index (CCI),[39] the Cumulative Illness Rating Scale (CIRS),[40] and the Older Americans Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire.[41] ACE-27,[42,43] CCI,[44–46] and CIRS[47,48] have also been used to determine treatment tolerance in older patients with cancer. In a study of 310 older patients (≥70 years) with head and neck cancer, comorbidity as measured by the ACE-27 index was an indicator of OS.[49] In a randomized trial that compared vinorelbine alone or in combination with gemcitabine in older patients with locally advanced non–small cell lung cancer (NSCLC), a CCI greater than 2 was associated with a higher risk of early treatment suspension (82% vs 30%, respectively).[44] In a phase III trial comparing platinum-doublet therapy as first-line treatment in patients with advanced-stage NSCLC, patients with severe comorbidities (as measured by CIRS) benefited from and tolerated platinum-doublet chemotherapy as well as patients with no comorbidities.[47] However, the former group had a higher risk of neutropenic fever and death from neutropenic infections.

More generally, a useful collection of tools to estimate the general mortality risk in the older adult can be found online at www.eprognosis.org. Life expectancy calculators available at this website could be used to determine anticipated life expectancy (independent of the cancer) and in clinical decision-making to assess whether the cancer is likely to shorten the patient's life expectancy or whether the patient is likely to become symptomatic from cancer during the

anticipated life expectancy. These calculators should be used in conjunction with clinical judgment.

Polypharmacy

Polypharmacy can be defined in various ways, including the use of an increased number of medications (5 or more), more than is clinically indicated; the use of potentially inappropriate medications; medication underuse; and medication duplication.[50] Although polypharmacy can be an issue across all age groups, it can be a more serious problem in older patients due to the presence of increased comorbid conditions treated with one or more drugs. In this patient population, the use of drugs for the management of cancer-related symptoms or side effects can result in polypharmacy.[51–53]

The use of multiple medications can lead to increased incidences of adverse drug reactions (which can lead to functional decline and geriatric syndromes), drug-drug interactions, and nonadherence.[54,55] Among patients with cancer receiving systemic anticancer therapy for solid tumors, one or more drug-drug interactions were observed in 27% of patients, which increased to 31% among patients with cancer receiving palliative care only.[55,56] Older patients, those with comorbid conditions, brain tumor patients, and those taking many medications are at greater risk of drug interactions.[56]

Alterations in pharmacokinetics and pharmacodynamics of drug metabolism in the older population can also contribute to adverse drug interactions.[57] Most of the commonly prescribed medications such as opioids, antidepressants, antibiotics, and antipsychotics, and anticancer drugs induce or inhibit cytochrome P-450 enzymes. In a retrospective analysis, Popa et al[58] assessed the impact of polypharmacy on toxicity from chemotherapy in 290 older patients (≥70 years). The results of this study demonstrated that cytochrome P-450 inhibition may contribute to nonhematologic toxicities, whereas hematologic toxicities may be associated with protein-binding interactions. The role of protein binding and cytochrome P-450 inhibition should be further explored.

The use of one or more potentially inappropriate medications among older patients has also been documented in several studies.[59–61] In one study, the use of inappropriate medications increased from 29% to 48% among patients with cancer in the palliative care setting.[60] In a more recent study of 500 older patients with cancer (≥65 years) starting a new chemotherapy regimen, polypharmacy (≥5 drugs) was observed in 48% of patients and the use of potentially inappropriate medications was seen in 11% to 18% of patients.[61] Although polypharmacy did not increase the risk of chemotherapy-related toxicity in this cohort, it was associated with a higher frequency of hospitalization and early discontinuation of chemotherapy.[61]

Evaluation of Polypharmacy: The guidelines recommend that medication review (prescription and over-the-counter medications, vitamins, and supplements) for duplication and appropriate use be done at every visit (see SAO-C, page 85). Beers criteria and the medication appropriateness index (MAI) are 2 of the most common approaches used to evaluate potentially inappropriate medication use in older patients. The screening tool of older persons' prescriptions (STOPP) and the screening tool to alert doctors to right treatment (START) criteria have been recently developed to evaluate drug interactions, medication duplication, and medication underuse.

Beers Criteria: The Beers' Criteria identify inappropriate medications that have potential risks that outweigh potential benefits based on the risk of toxicity and the presence of potential drug-disease interaction in older patients with cancer.[62,63] The criteria are appropriate for persons older than 65 years of age and provide a rating of severity for adverse outcomes and a descriptive summary of the prescribing information associated with the medication. The updated 2003 Beers Criteria have been used to evaluate polypharmacy in older patients with cancer both in an oncology-specific acute care unit (oncology-acute care for elders [OACE]; n=47 with a median age of 73.5 years) and in the outpatient setting (n=154 with a median age of 74 years).[64,65] The Beers Criteria-based polypharmacy was observed in 21% and 11% of patients, respectively. Both of these studies had implemented medication review and pharmacist-based interventions to improve the appropriateness of prescribing. In the OACE study, 53% had a subsequent alteration in their medication regimen and 28% had a potentially inappropriate medication discontinued, after implementation of recommendation by the OACE team.[64] In the outpatient study, after geriatric management evaluation, 50% of patients required specific interventions, and the use of

potentially inappropriate medication was identified in 11% of patients.[65]

The Beers' Criteria were updated by the American Geriatrics Society (AGS) in 2012 to improve monitoring of drug use, e-prescribing, interventions to decrease adverse events in older adults, and patient outcomes.[66] In the updated criteria, medications that are used in older adults are divided into 3 categories: 1) potentially inappropriate medications to avoid in older adults; 2) potentially inappropriate medications to avoid in older adults with certain diseases and syndromes that the listed drugs can exacerbate; and 3) medications to be used with caution in older adults.

MAI: MAI was developed to measure appropriate prescribing based on a 10-item list and a 3-point rating scale.[67] Samsa et al[68] subsequently modified the MAI to include a single summated MAI score per medication that demonstrated acceptable reliability in assessing medication appropriateness among 1644 medications prescribed to 208 older veterans from the same clinic. This modified MAI appears to be a valid and relatively reliable measure to detect medication appropriateness and inappropriateness in the community pharmacy setting and in ambulatory older patients on multiple medications.[69,70] MAI scores were significantly lower for medications with a high potential for adverse effects compared with those with a low potential (1.8 vs 2.9).[69] Higher MAI scores were also associated with lower self-reported health scores in older adults.[71] MAI has not been evaluated extensively in older patients with cancer.

STOPP/START Criteria: STOPP/START criteria were established using the Delphi consensus process by an 18-member expert panel from the academic centers of Ireland and the United Kingdom.[72] The STOPP criteria is composed of 65 indicators for potentially inappropriate prescribing, including drug–drug and drug-disease interactions, therapeutic duplication, and drugs that increase the risks of geriatric syndromes, whereas the START criteria incorporate 22 evidence-based indicators to identify prescribing omissions in older people.[73,74] In a randomized trial of 400 hospitalized patients (≥65 years), unnecessary polypharmacy, the use of drugs at incorrect doses, and potential drug-drug and drug-disease interactions were significantly lower in the group assigned to screening with STOPP/START criteria with recommendations provided to their attending physicians compared with the control group assigned to routine pharmaceutical care.[75] Significant improvements in prescribing appropriateness were sustained for 6 months after discharge.

Nutritional Status

Nutritional deficiency or malnutrition is a common and serious condition in older patients. Although some malnutrition is attributable to the underlying illness, in most patients it is due to inadequate intake of calories. The Mini-Nutritional Assessment (MNA) has been designed and validated to provide a single, rapid assessment of nutritional status in older patients in the outpatient settings (see SAO-C, page 93).[76,77] MNA is composed of simple measurements and brief questions that help to identify people at risk for malnutrition before severe changes in weight or albumin levels occur. Rubenstein et al[78] have developed a shortened version of MNA, which also has good diagnostic accuracy. Special attention should also be devoted to vitamin D deficiency since that may be related to osteoporosis and fractures.[79]

Cognitive Function

Older patients with cancer who are cognitively impaired have an increased risk of functional dependence, a higher incidence of depression, and a greater risk of death. Cognitive function is also predictive of medication nonadherence across diagnoses, regardless of the complexity of regimen.[80] Cognitively impaired patients should be cared for by an experienced multidisciplinary geriatric oncology team along with good supportive care throughout the treatment.[81] In addition, the association between cognitive impairment and the ability to weigh the risks and benefits of cancer treatment decisions needs to be considered.

The use of certain classes of medications (anticholinergics, antipsychotics, benzodiazepines, corticosteroids, and opioids) has also been associated with cognitive impairment in older adults.[82–84]

Antipsychotic drugs are also associated with higher mortality rates in patients with dementia.[85–87] Hilmer et al[88] have developed a drug burden index, which is a useful evidence-based tool for assessing the effect of medications on the physical and cognitive performance in older adults. Special considerations for over- or underuse, duration of therapy, and dosage should be in place with the use of these classes of medications.

For patients with suspected impaired cognitive

function that could potentially interfere with their decision-making capacity, the guidelines recommend consultation with a clinician experienced in cognitive evaluation (geriatrician, neurologist, geriatric psychiatrist, or neuropsychologist) or initiation of further evaluation to determine the appropriate diagnosis (eg, mild cognitive impairment, dementia, delirium).[89] In addition to the clinical observation by the medical team, any concerns reported by the patient or the patient's family suggestive of an impaired cognitive function should also trigger further evaluation. The NCCN Guidelines recommend periodic reassessment of cognitive function or when considering changes to treatment plan for all patients including those with no cognitive impairment (see SAO-E, page 95).

See "Geriatric Syndromes" below for the assessment of dementia and delirium in older patients with cancer.

Socioeconomic Issues

Social ties have been identified as significant predictors of mortality in older adults.[90,91] In a study of 2835 women diagnosed with breast cancer, socially isolated women had an elevated risk of mortality after a diagnosis of breast cancer.[92] An evaluation of social support is an integral part of geriatric assessment. The patient's treatment goals should be discussed with them. In addition, the patient's living conditions, presence, and adequacy of caregiver and financial status should also be taken into consideration. Consultation with a social worker should be encouraged. Consultation with a financial expert to discuss the cost and coverage options of treatment would also be beneficial.

Geriatric Syndromes

Dementia, delirium, depression, distress, osteoporosis, falls, fatigue, and frailty are some of the most common syndromes in older patients with cancer.[93] Dementia and delirium are 2 of the most common causes of cognitive impairment.[94] Older patients with cancer experience a higher prevalence of geriatric syndromes than those without cancer. In an analysis of a national sample of 12,480 community-based elders, 60.3% of patients with cancer reported one or more geriatric syndromes compared with 53.2% of those without cancer.[95] In this cohort, the prevalence of hearing trouble, urinary incontinence, falls, depression, and osteoporosis were significantly higher in patients with cancer than those without cancer.

Dementia

Dementia is a progressive condition characterized by impairment of memory and at least one other cognitive function impairment (eg, aphasia, apraxia, agnosia, executive function loss) that would interfere with the ability to perform daily functions independently. Dementia is often present in older patients as a comorbid condition. In a SEER database analysis, older patients with colon cancer (≥67 years) and dementia were less likely to receive invasive diagnostic methods or therapies with curative intent.[96] Preexisting dementia was also associated with high mortality, mostly from noncancer causes, in patients 68 years or older diagnosed with breast, colon, or prostate cancer.[97] Mild cognitive impairment is an intermediate state between normal cognition and dementia. It is characterized by subjective memory impairment, preserved general cognitive function, and intact ability to perform daily functions.[98]

Blessed Orientation-Memory-Concentration (BOMC) test, Mini-Mental State Exam (MMSE), and the Montreal Cognitive Assessment (MoCA) have been used to screen for cognitive impairment in older adults.[99–102] BOMC is a 6-item test that has been shown to discriminate among mild, moderate, and severe cognitive deficits.[99] MMSE is an 11-item screening test that quantitatively assesses the severity of cognitive impairment and documents cognitive changes occurring over a period of time.[100,101] However, MMSE is not adequate for mild cognitive impairment and does not predict future decline. MoCA is a brief screening tool with high sensitivity and specificity for detecting mild cognitive impairment in patients performing in the normal range on the MMSE.[102] MoCA has been shown to be a superior prognostic indicator than the MMSE in patients with brain metastases.[103,104] In a feasibility study of MoCA in patients with brain metastases, cognitive impairment was detected in 80% of the patients by the MoCA compared with 30% by the MMSE.[103] Among the 28 patients with a normal MMSE, 71% had cognitive impairment according to the MoCA.

Clinical interview with cognitive and functional assessment to screen for mild cognitive impairment or dementia is recommended for all patients, because there is a strong correlation between decline in cognitive status and the loss of functional independence in older adults.[105] The guidelines have included Mini-Cog as a screening tool for the assess-

ment of mild cognitive impairment and dementia in older patients with cancer. Mini-Cog is a 5-point test (consisting of a 3-word recall and clock drawing test) used for screening cognitive impairment in the older population.[106,107] Assessment of cognitive function can also be confounded by fatigue, depression, anxiety, underlying brain tumors, endocrine dysfunction, nutritional deficiency, alcohol use, and sleep disturbances.[108] Therefore, if dementia is suspected, further evaluation, including brain imaging neuropsychologic testing and evaluation for vitamin B_{12} deficiency and thyroid dysfunction may be indicated. For patients with mild cognitive impairment, the guidelines recommend reassessment of cognitive function periodically or when considering changes to treatment plan.

Delirium

Delirium is an acute decline in attention and cognition over a short period of time (usually hours to days) and is characterized by the disturbance of consciousness with reduced ability to focus, sustain, or shift attention.[109] It is an underrecognized problem in older adults and can contribute to poorer clinical outcome and functional decline, and it can impair communication between the patient and physicians for patients with advanced cancer.[110] Dementia is the leading factor for delirium and about two thirds of cases of delirium occur in older patients with dementia.[109]

The Confusion Assessment Method (CAM) is a screening and diagnostic tool based on 4 important features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.[111,112] The Memorial Delirium Assessment Scale is a 10-item validated instrument developed for repeated use to quantify the severity of delirium symptoms in patients with advanced cancer.[113] The Nursing Delirium Screening Scale is an observational 5-item scale and has been validated in the oncology inpatient setting and is associated with high sensitivity and specificity.[114]

The Hospital Elder Life Program (HELP) includes interventions for the management of 6 risk factors for delirium (cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment).[115] In the Yale Delirium Prevention Trial (N=852), the HELP interventions resulted in a significant reduction in the development of delirium, total number of days with delirium, and the total number of delirium episodes in hospitalized patients 70 years or older.[116]

The NCCN Guidelines have included CAM as a screening tool for delirium. Evaluation and treatment of all potential causes of delirium is recommended for all patients with delirium. Medications that can contribute to delirium should be used with caution in older patients with cancer.[117–119]

Depression

The Geriatric Depression Scale (GDS) is a reliable and valid tool for screening for depression in older patients with no cognitive impairment and in patients with mild to moderate cognitive impairment.[120] GDS was originally developed by Yesavage et al[120] as a 30-item scale. Recently, shortened versions of GDS have been found equally accurate and less time consuming in screening for depression in older adults.[121,122] Cancer-related fatigue and depression frequently occur together; therefore, patients reporting fatigue should probably be assessed for depression.[123–125]

Distress

Psychologic distress is common among patients with cancer. Hurria et al[126] reported that significant distress was identified in 41% of patients 65 years or older with cancer, and poorer physical function was the best predictor of distress. Screening tools have been found effective and feasible in reliably identifying distress and the psychosocial needs of patients.[127–129] The NCCN distress thermometer (DT) and the accompanying 36-item problem list is a well-known screening tool, specifically developed for patients with cancer by the NCCN Distress Management Panel.[130,131] The NCCN DT has been validated by several studies in patients with different types of cancer and has revealed good correlation with the more comprehensive Hospital Anxiety and Depression Scale.[129] Patients can quickly fill out the NCCN DT screening tool in the waiting room, and the tool can alert the physician to potential problems. This tool identifies whether patients with cancer have problems in 5 different categories: practical, family, emotional, spiritual/religious, and physical. See the NCCN Guidelines for Distress Management (to view the most recent version of these guidelines, visit NCCN.org) for more information on the use of the NCCN DT as a screening tool in patients with cancer.

Frailty

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, causing vulnerability to adverse

outcomes.[132] Frail patients are at risk for falling, disability, hospitalization, and death. Fried Frailty Criteria and the Balducci Frailty Criteria are the 2 most common measures used to identify frail patients.[133,134] According to Fried Frailty Criteria, frailty is defined as the clinical syndrome with 3 or more of the following conditions: unintentional weight loss (≥10 lb in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity.[133] In a prospective, observational study of 5317 men and women (≥65 years), frailty status based on these criteria was found to be predictive of incident falls, worsening mobility or ADL function, incidence of hospitalization, and death.[133]

Balducci Frailty Criteria are based on the components of CGA (dependence in ≥1 ADLs, ≥3 comorbid conditions, and ≥1 geriatric syndromes).[134] These CGA frailty criteria have been found to be more useful in identifying frail patients with cancer.[135,136] In a prospective study that compared the Balducci Frailty Criteria and the modified version of Fried Frailty Criteria in 176 patients (age 70–94 years) who underwent elective surgery for colorectal cancer, although both frailty measures were predictive of OS, Balducci Frailty Criteria were more useful than the modified version of Fried Frailty Criteria in predicting postoperative complications.[136]

Fatigue

Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning. In advanced cancer, the prevalence of fatigue is greater than 50% to 70%.[137] In a study that evaluated the prevalence of common symptoms in patients with advanced cancer, fatigue was independently associated with chemotherapy, hemoglobin level, and other symptoms such as pain and depression.[138] Patients perceive fatigue to be one of the most distressing symptoms associated with cancer and its treatment; fatigue is more distressing than pain or nausea and vomiting.[139,140] In contrast to normal fatigue, cancer-related fatigue is refractory to sleep and rest, perhaps because patients with cancer often have aberrant sleep patterns. It is reasonable to expect that fatigue may precipitate functional dependence, especially in patients who are already dependent in IADLs.[141–143]

Multiple factors can contribute to fatigue, including pain, emotional distress, anemia, comorbidities, and/or sleep disturbance; many of them are treatable. Certainly, the best strategy is avoidance of any fatigue that may precipitate functional dependence in older adults. Energy conservation, exercise programs, stress management, sleep therapy, and psychostimulants are some of the interventions that have proved valuable. Screening for fatigue can be done using a brief screening questionnaire that would enable patients to rate the severity of their fatigue on a scale of 0 (no fatigue) to 10 (worst fatigue). See the NCCN Guidelines for Cancer-Related Fatigue (to view the most recent version of these guidelines, visit NCCN.org).

Falls

Falls are one of most common geriatric syndromes. Risk factors include arthritis; depressive symptoms; orthostasis; impairments in muscle strength, cognition, vision, balance, or gait; and the use of 4 or more prescription medications.[144] The use of inappropriate medications (especially hypnotics, sedatives, antidepressants, long-acting benzodiazepines and other inappropriate psychotropics, and medications with anticholinergic properties) is associated with an increased risk of falls in older adults (≥65 years).[145,146] Furthermore, cancer diagnosis (especially in the first 6 months after diagnosis) and chemotherapy are also associated with a high risk of falls.[147,148] In a prospective study of 185 patients with advanced cancer, more than 50% of patients experienced falls associated with a high risk of physical injury, regardless of age; the incidences of falls were 53% among patients younger than 65 years and 49% among those 65 years or older.[148] Median time to fall was 96 days. In a multivariate analysis, the diagnosis of primary brain tumor or brain metastasis, number of falls in the preceding 3 months, severity of depression, benzodiazepine dose, and cancer-related pain were identified as independent risk factors.[148] Another recent study also reported that the risk of falls increases with each cycle of chemotherapy and that patients treated with taxane-based chemotherapy may be at greater risk of falls than those treated with platinum-based chemotherapy.[149]

The AGS/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons recommends a multifactorial risk assessment followed by multicomponent interventions to address the identified risks and prevent falls in patients 75 years or older with 2 or more falls in the past 12 months or difficulty with walking or balance or gait difficulties.[150] Recommended interventions include

minimizing the number of medications; providing a tailored exercise program to improve strength, balance, gait, and coordination; treating vision impairment (including cataracts); managing postural hypotension, heart rate, and rhythm abnormalities and foot and footwear problems; supplementing with vitamin D; modifying the home environment; and providing education and necessary information.[150]

Multifactorial risk assessment and management, exercise, vitamin D supplementation, withdrawal of psychotropic medications, and environmental modifications have been shown to be effective in reducing the risk and/or rate of falls in older patients.[151–156] The guidelines recommend assessment of history of falls, balance, and gait difficulties for all patients (see SAO-D, page 94). Assessment of gait using the TUG test, evaluation for physical or occupational therapy, vitamin D supplementation (in patients with low levels of vitamin D), or referral to geriatrics or a primary care physician can be considered for patients who have experienced a fall in the last 6 months or who are afraid of falling.

Osteoporosis

Osteoporosis and its associated increased risk of fracture is a major risk factor in patients with cancer, especially in women receiving chemotherapy or hormonal therapy for breast cancer and in men receiving hormonal therapy for prostate cancer. Osteoporosis can be prevented with appropriate screening, lifestyle interventions, and therapy. The diagnosis of osteoporosis is based on assessment of bone density by a dual energy x-ray absorptiometry scan. Management of bone health has become an integral part of comprehensive cancer care. Older patients should be made aware of the impact of cancer therapies on bone health and should adhere to treatment recommendations for maintaining bone health.[157] The NCCN Task Force Report on Bone Health in Cancer Care discusses effective screening and therapeutic options for the management of treatment-related bone loss.[158]

Application of CGA for Patients with Cancer

The feasibility of CGA has been demonstrated in older patients with cancer.[134,159,160] Balducci and Extermann[134] studied CGA in the older patient with cancer including an evaluation of functional status, comorbidity, socioeconomic conditions, cognitive and emotional function, nutritional status, polypharmacy, and geriatric syndromes.[134] Ingram et al[159] used a self-administered CGA including demographics, comorbid conditions, functional status, pain, financial well-being, social support, emotional state, spiritual well-being, and quality of life to characterize older patients with cancer. Repetto et al[160] demonstrated that CGA adds substantial information on the functional assessment of older patients with cancer (≥65 years). Among patients with a good performance status, 13% had 2 or more comorbidities; 9.3% and 37.7% had ADL or IADL limitations, respectively.

CGA components (comorbid conditions, functional status, cognitive function, geriatric syndromes, and nutritional status) have been associated with the type of cancer treatment and survival in older patients with cancer.[24–26,161–165] For example, in women aged 65 years or older diagnosed with stage I to III primary breast cancer, the all-cause and breast cancer-specific death rate at 5 and 10 years was consistently approximately 2 times higher in women with 3 or more cancer-specific CGA deficits, regardless of age and stage of disease.[161] In another prospective study of 375 consecutive older patients with cancer (ELCAPA study), in a multivariate analysis, a lower ADL score and malnutrition were independently associated with cancer treatment changes.[162] In a recent prospective multicenter study of 348 previously untreated patients with cancer older than 70 years, Soubeyran et al[163] identified poor nutritional status, impaired mobility, and advanced tumors as risk factors predictive of early death (<6 months) after initiation of chemotherapy. In a phase III study (FFCD 2001-02), impairment in functional status and cognitive function (as assessed by IADL and MMSE, respectively) were predictive of severe chemotherapy toxicity and hospitalization in older patients with metastatic colorectal cancer.[164] Similarly, among older patients receiving induction chemotherapy for acute myeloid leukemia (AML), OS was significantly shorter for patients with impaired cognitive and physical function.[165] CGA has also been reported to be an efficient method to identify older patients with diffuse large B-cell lymphoma who can benefit from anthracycline-based chemoimmunotherapy.[26,135,166]

Although CGA is helpful for physicians to develop a coordinated plan for cancer treatment and to guide appropriate interventions to the patient's

problems, it can be time consuming and may not be practical for all patients. Some investigators have developed a brief but comprehensive geriatric assessment specific for older patients with cancer, while others have reported a 2-step approach using frailty screening tools to identify older patients who would benefit from a CGA.[167,168]

The cancer-specific geriatric assessment (CSGA) developed by Hurria et al[167] includes assessment of older patients with cancer across 7 domains (functional status, comorbidity, polypharmacy, cognitive function, psychological status, social functioning and support, and nutritional status) using validated measures. The feasibility of CSGA was demonstrated in a pilot study of 43 patients with cancer (median age, 74 years), most of whom had advanced-stage disease. This brief geriatric assessment is largely self-administered and can be completed by most older patients without assistance. Recent results from the CALGB 360401 study also demonstrated the feasibility of including CSGA in future cooperative group clinical trials.[169] A multicenter study involving 500 older patients (median age, 73 years) with cancer also showed that CSGA is useful for predicting treatment-related toxicity in older patients with solid tumors.[170]

The Senior Adult Oncology Program 2 (SAOP2) screening tool developed by Extermann[171] is aimed at identifying older patients who would benefit from a multidisciplinary evaluation by a geriatric oncology team. The SAOP2 screening tool includes assessment of older patients with cancer across the following domains using validated measures: self-rated health, cognitive function, nutritional status, comorbidity, ECOG performance status, and functional status.

Abbreviated CGA (aCGA),[172,173] Barber questionnaire,[174] Fried Frailty Criteria,[133,175] Geriatric 8 (G-8),[176–178] Groningen Frailty Index,[173] Triage Risk Screening Tool (TRST),[178] Vulnerable Elders Survey (VES-13),[177,179–182] and Lachs' screening test[183] have been used to determine if a CGA would be beneficial for older patients with cancer. G-8 and aCGA were developed specifically for older patients with cancer. In a recent systematic review, Hamaker et al[168] assessed the sensitivity and specificity of frailty screening methods that could potentially be useful in the selection of patients for CGA. G-8 and TRST had the highest sensitivity (87% and 92%, respectively) and aCGA had the highest specificity (97%) for predicting frailty on CGA. Although all of the screening tools included the assessment of functional status, the assessment of other domains such as psychosocial status, nutritional status, comorbidities, and polypharmacy varied widely. For example, aCGA, Fried Frailty Criteria, and the VES-13 had a stronger predictive value for impairment of functional status (ADLs and IADLs) and G-8 had a strong predictive value for nutritional status but not for other geriatric conditions. As a result, none of the screening tools were successful in identifying impairments across all of the domains included in the CGA. Given the lack of data supporting the efficacy of any one screening tool for predicting outcome of a CGA, it would be beneficial to assess all older patients with a CGA before starting therapy.

Approach to Decision-Making in Older Patients With Cancer

The risk of morbidity from cancer is generally established by the stage at diagnosis, the aggressiveness of the tumor, and risk of recurrence and progression. After initial screening and CGA, patients with a low risk of dying or suffering from cancer during their lifetime can receive symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care (to view the most recent version of these guidelines, visit NCCN.org). Patients in the moderate- or high-risk group can be further evaluated to assess their functional dependency, decision-making capacity, overall goals, and desire for proposed treatment (see SAO-1, page 84).[184,185]

A patient's decision-making capacity is generally evaluated based on the patient's ability to understand the relevant information about the diagnosis and proposed diagnostic tests or treatment; appreciate his or her underlying values and current medical situation; use reason to make a decision; and communicate his or her choice. Sessums et al[184] recently evaluated a variety of instruments used to assess medical decision-making capacity in adult patients without any mental illness and concluded that Aid to Capacity Evaluation (ACE) is the best available instrument to assist physicians in making assessments about a patient's medical decision-making capacity. Irrespective of age, a person who is function-

ally independent without serious comorbidities and has the decision-making capacity should be a good candidate for most forms of cancer treatment. In patients without decision-making capacity, the guidelines recommend considering consultation from an ethics committee or social worker. Additional information can be obtained from the patient's proxy, advanced directive, health care power of attorney, or clinician's documentation.

Functionally independent patients with contraindications to treatment and patients with major functional impairment with or without complex comorbidity should be managed according to the appropriate NCCN Guidelines for Supportive Care (available online at NCCN.org). Patients who are dependent in some IADLs, with or without severe comorbidities, are at increased risk of treatment complications. For these patients with intermediate functional impairment who have milder problems (such as dependence in one or more IADLs, milder comorbidity, depression, minor memory disorder, mild dementia, and inadequate caregiver), treatment may still be administered with special individualized precautions.[4]

The potential benefits of cancer treatment include prolonged survival, maintenance, improvement of quality of life and function, and palliation of symptoms. For patients who are able to tolerate curative treatment, options include surgery, radiation therapy (RT), chemotherapy, and targeted therapies. Symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care (available online at NCCN.org) are recommended for all patients.

Surgery

In general, age is not a primary consideration for surgical risk, although the physiologic status of the patient needs to be assessed (see SAO-3, page 86). Performance status and comorbidities are more important factors than age when considering surgical treatment options for older adults.[186] The American College of Surgeons and the AGS have provided general guidelines for the preoperative assessment of older patients undergoing surgery. These guidelines could also be applied to older patients with cancer undergoing surgery.[119]

The Surgical Task Force report from SIOG (International Society of Geriatric Oncology) reported that in many malignancies (breast, gastric, and liver), surgical outcomes in older patients with cancer were not significantly different from their younger counterparts.[187] Preoperative Assessment of Cancer in the Elderly (PACE) was developed to determine the suitability of older patients for surgical intervention.[188] PACE incorporates CGA, brief fatigue inventory, performance status, and American Society of Anesthesiologists (ASA) grade. In an international prospective study, 460 consecutive older patients completed PACE before surgery.[189,190] In a multivariate analysis, moderate-to-severe fatigue, a dependent IADL, and an abnormal performance status were identified as the most important independent predictors of postoperative complications. Disability assessed by ADLs, IADLs, and performance status were associated with an extended hospital stay.

Patients should be made aware that emergency surgery carries increased risk of complications. After surgery, physical or occupational therapy should be considered to expedite the patient's return to their preoperative functional level. Impaired cognitive function is also a risk factor for postoperative complications, prolonged hospital stay, and 6-month overall postoperative morbidity.[191,192] Older age is also a risk factor for postoperative delirium. The HELP[115,116] and NICE guidelines[193] provide recommendations for the management of delirium in hospitalized patients 70 years or older.

RT

RT (external-beam or brachytherapy) can be offered either in the curative or in the palliative setting.[194] Hypofractionated RT may be an alternative treatment option in patients who are unable to tolerate conventional dose RT.[195] Available data from the literature indicate that RT is highly effective and well tolerated and that age is not a limiting factor in older patients with cancer.[196–198] However, concurrent chemoradiation, should be used with extreme caution; dose modification of chemotherapy may be necessary to reduce toxic side effects. Nutritional support and pain control for RT-induced mucositis are recommended for patients receiving RT (see SAO-3, page 86).

Chemotherapy

Several retrospective studies have reported that the toxicity of chemotherapy is not more severe or prolonged in persons older than 70 years.[199–203] However, the results of these studies cannot be generalized for the following reasons:

- Only a few patients were 80 years or older; therefore, minimal information is available on the oldest patients.
- The older patients involved in these studies were highly selected by the eligibility criteria of the cooperative group protocols and were not representative of the general older population, because they were probably healthier than most older patients.
- Many of the treatment regimens used in these trials had lower dose intensity than those in current use.
- Nevertheless, these studies are important, because they demonstrate that age, by itself, is not a contraindication to cancer chemotherapy. Therefore, patient selection is extremely important to maximize the benefits of adjuvant chemotherapy in older patients with breast cancer, colon cancer, and NSCLC.

Increased age has been associated with changes in the pharmacokinetics and pharmacodynamics of cancer therapy and increased susceptibility of normal tissues to toxic complications. In general, all these changes increase the risks of chemotherapy.[204] Pharmacodynamic changes of interest include reduced repair of DNA damage and increased risk of toxicity. Pharmacokinetic changes of major concern include decrease in the glomerular filtration rate (GFR) and volume of distribution of hydrosoluble drugs. Although the hepatic uptake of drugs and the activity of cytochrome P450 enzymes also decrease with age, the influence of these changes on cancer chemotherapy is not clear. Intestinal absorption may decrease with age, but it does not appear to affect the bioavailability of anticancer agents. The pharmacokinetics of antineoplastic drugs is unpredictable to some extent; thus, drug doses should be adjusted according to the degree of toxicity that develops. However, adequate dosing is necessary to ensure the effectiveness of therapy.

Extermann et al[205] devised the MAX2 index for estimating the average per-patient risk for toxicity from chemotherapy. In a retrospective analysis, Shayne et al[206] identified advanced age (≥65 years), greater body surface area, comorbidities, anthracycline-based regimens, a 28-day schedule, and febrile neutropenia as independent predictors of reduced dose intensity among patients with early-stage breast cancer receiving adjuvant chemotherapy. In another retrospective analysis of older patients (≥65 years) with invasive breast cancer, the type of adjuvant chemotherapy regimen was a better predictor of toxicity than increased age or comorbidity score.[45] An anthracycline-based regimen resulted in greater grade 3 or 4 toxicity, hospitalization, or febrile neutropenia, whereas treatment delays due to myelosuppression were more frequent with the cyclophosphamide-containing regimen. Among older patients with ovarian cancer, those receiving standard-dose chemotherapy were more likely to experience cumulative toxicity and delays in therapy.[46]

Other investigators have developed tools incorporating components of CGA to assess the individual risk of severe toxicity from chemotherapy in older patients.[23,170,207] In a study of 83 older patients with advanced ovarian cancer treated with carboplatin and cyclophosphamide, Freyer et al[23] identified comorbidities (symptoms of depression at baseline), functional dependence, and polypharmacy (>6 different medications per day) as independent predictors of severe toxicity and OS. Hurria et al[170] developed a scoring algorithm for predicting chemotherapy toxicity in older patients with cancer. The following factors were predictive of grade 3 to 5 chemotherapy toxicity: 1) age 72 years or older; 2) cancer type (gastrointestinal or genitourinary); 3) standard dosing of chemotherapy; 4) polychemotherapy; 5) hemoglobin (male: <11g/dL; female: <10g/dL); 6) creatinine clearance less than 34 mL/min (Jelliffe formula using ideal weight)[208]; 7) hearing impairment described as fair or worse; 8) one or more falls in last 6 months; 9) limited in walking one block; 10) the need for assistance with taking medications; and 11) decreased social activities because of physical or emotional health.[170] Extermann et al[207] developed the chemotherapy risk assessment scale for high-age patients score, which could be useful in predicting significant differences in the risk of severe toxicity in older patients with cancer starting a new chemotherapy. In this model, diastolic blood pressure, IADLs, lactate dehydrogenase, and type of therapy were the best predictors of hematologic toxicity. Performance status, cognitive function, nutritional status, and type of therapy were the best predictors of nonhematologic toxicity.

Side Effects of Chemotherapy: In older patients undergoing chemotherapy, the most common complications include myelosuppression resulting in neu-

tropenia, anemia, or thrombocytopenia; mucositis; renal toxicity; cardiac toxicity; and neurotoxicity (see SAO-4, page 87). Older patients appear to be at special risk for severe and prolonged myelosuppression and mucositis, increased risk for cardiomyopathy, and increased risk for central and peripheral neuropathy. In addition, they are also at risk for infection (with or without neutropenia), dehydration, electrolyte disorders, and malnutrition either as a side effect of the chemotherapy or directly from the tumor. Chemotherapy can also affect cognition, function, balance, vision, hearing, continence, and mood.[94] The combination of these complications enhances the risk of delirium and functional dependence. It is essential to detect and correct these complications (that may interfere with treatment) in order to achieve maximum benefit from chemotherapy.

See the discussion section of the complete guidelines at NCCN.org for the prevention and/or amelioration of some of the common chemotherapy-related complications.

Targeted Therapy

The emergence of targeted therapies (monoclonal antibodies and small molecules targeted against specific molecular pathways required for the development of a particular malignancy) has significantly improved outcomes in a variety of malignancies. The use of targeted therapies in older patients appears to be promising in view of their better efficacy and toxicity than conventional chemotherapeutic agents.[209,210] However, these drugs are also associated with some unique and severe toxicities.[211] For example, cardiovascular complications such as left ventricular dysfunction are associated with HER2 inhibitors (eg, trastuzumab), hypertension and arterial thromboembolic events are associated with vascular endothelial growth factor receptor inhibitors (eg, bevacizumab),[212–214] whereas dermatologic toxicities (acneiform rash and hand-foot skin reaction) are the major adverse effects of epidermal growth factor receptor inhibitors (eg, erlotinib, sunitinib, sorafenib, cetuximab).[215]

There are limited but growing data available on the toxicity safety and efficacy of targeted therapies in older patients with cancer. Prospective clinical trials that include a sufficiently large number of older patients are needed to accurately determine the efficacy and tolerability of targeted therapies in this cohort of patients. In patients who are not able to tolerate cytotoxic chemotherapy, the risk-benefit ratio should be considered before starting targeted therapy, and the use of targeted therapies should be individualized.

Adherence to Therapy

Adherence to the prescribed regimen, especially oral therapy, is essential to derive maximal clinical benefit. Although older age per se is not a consistent risk factor for nonadherence, older adults are at an increased risk for nonadherence for a variety of reasons, including cognitive impairment, increased number of comorbid conditions, polypharmacy, higher risk of side effects adversely affecting comorbidities, increased likelihood of drug interactions, limited insurance coverage, social isolation, and inadequate social support.[216]

Discontinuation and nonadherence to adjuvant hormonal therapy is well documented in women with early-stage breast cancer.[217] In studies that have evaluated adherence to adjuvant hormonal therapy among older women (≥55 years) diagnosed with early-stage breast cancer, the reported rates of nonadherence or discontinuation range from 15% to 49%.[218–221] In a cohort of 961 women (≥65 years) diagnosed with early-stage estrogen receptor-positive or indeterminate breast cancer, Owusu et al[221] reported a discontinuation rate of 49% before the completion of 5 years. Women aged 75 years or older, those with an increase in CCI, and those with an increase in the number of cardiopulmonary comorbidities at 3 years from diagnosis, those with an indeterminate estrogen receptor status, and those who had received breast-conserving surgery without RT were at higher risk of discontinuation.[221] Women with estrogen receptor-negative and node-positive disease, those who report severe initial side effects (depression, nausea, visual complaints, and vaginal bleeding), and women with neutral or negative beliefs about the value of hormonal therapy are also more likely to discontinue therapy.[218–220]

Adherence to adjuvant chemotherapy has also been evaluated in older patients with early-stage breast cancer.[222–224] In the randomized study (CALGB 49907) that evaluated adjuvant chemotherapy with oral capecitabine versus standard chemotherapy in 161 women (≥65 years) with early-stage breast cancer, 25% of the patients took fewer than 80% of the planned doses.[223] Nonadherence was more likely among women with node-negative disease and mas-

tectomy. Adherence was not related to age, tumor stage, or hormone receptor status. However, in other studies, poor adherence to adjuvant chemotherapy was more frequent in older patients (≥65 years).[222,224]

Although nonadherence to adjuvant chemotherapy was not associated with shorter RFS in the CALGB 49907 study (may be due to limited sample size), other studies have reported inferior clinical outcomes in patients with nonadherence to cancer therapy.[225–228] Among 8769 women treated with adjuvant hormone therapy for stage I to III breast cancer, Hershman et al[225] identified early discontinuation and nonadherence to adjuvant hormonal therapy as independent predictors of increased mortality. At a median follow-up of 4 years, the estimated 10-year survival rates were 80.7% and 73.6%, respectively, for women who continued hormonal therapy and those who discontinued therapy ($P<.001$). For those who continued, the 10-year survival rate was higher for women with adherence to therapy than for those with nonadherence (81.7% and 77.8%, respectively; $P<.001$). In the ADAGIO study, nonadherence was associated with poorer response to imatinib in patients with CML; nonadherence rates were significantly higher for patients with suboptimal response compared with those with optimal response to imatinib (23% and 7%, respectively).[226] Marin et al[227] also identified adherence as the only independent predictor for achieving complete molecular response on standard-dose imatinib in patients with CML. Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.[228]

Treatment-related adverse events, complexity of regimens, and poor understanding of the need for treatment and the consequences of nonadherence are some of the common barriers to adherence. In a multicenter, prospective, open-label randomized trial of exemestane versus letrozole (n=503), 32.4% discontinued initial therapy within 2 years because of adverse effects, and the median time to treatment discontinuation was 6 months.[229] In a recent survey of women taking oral hormonal therapy for breast cancer, prior knowledge about the impact of adherence on clinical outcomes and better management of treatment-related side effects were indicated as the most important factors for increasing compliance.[230]

In older patients with cancer, assessment of risk factors for nonadherence is recommended when considering a treatment regimen that will include an oral agent (see SAO-F, page 97). Close monitoring of patient adherence, reducing regimen complexity (if possible), interventions designed to educate older patients about the risks and benefits of oral therapy and the importance of adherence to therapy, adequate and appropriate management of side effects, and scheduling follow-up at regular intervals to review the side effects are some of the strategies that may be helpful to minimize nonadherence.

Disease-Specific Issues

Because the biologic characteristics of certain cancers are different in older patients compared with their younger counterparts and partly because of older adults' decreased tolerance of treatment, chemotherapy should be individualized based on the nature of the disease and the performance status of the patient.

Disease-specific issues related to age in hematologic malignancies are discussed in the next section. See the discussion section of the complete guidelines at NCCN.org for the disease-specific issues related to age in other cancer types.

Hematologic Malignancies

Acute Lymphoblastic Leukemia: Acute lymphoblastic leukemia (ALL) in older patients is characterized by a lower incidence of T-cell ALL and the presence of unfavorable chromosomal abnormalities, both of which have been identified as poor prognostic factors.[231,232] It is strongly recommended that older patients with ALL be treated in a specialized center.

In older patients, intensive multiagent chemotherapy regimens have been associated poor OS, in spite of favorable response rates after induction therapy.[233–235] In an analysis of 268 patients (≥60 years) with newly diagnosed ALL, induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) induced an overall complete response (CR) in 65% of patients.[234] However, the 3-year OS rate was less than 10%. In a multicenter prospective study that evaluated age-adapted induction chemotherapy followed by maintenance therapy with interferon and chemotherapy, 85% of patients 55 years or older had a CR after completion of induction therapy with a median OS, and DFS was only 14 months.[235] The inferior outcomes have been attributed to treatment-

related mortality (7.5%) during induction and more-resistant disease. A recent randomized phase II trial (GRAALL-SA1) showed that with the use of pegylated doxorubicin in combination with vincristine and dexamethasone, pegylated doxorubicin did not result in any survival benefit over doxorubicin, despite its better toxicity profile (lower risk of cardiotoxicity and myelosuppression), due to a higher rate of induction failure (17% vs 3%; *P*=.10) and a higher cumulative incidence of relapse (52% vs 32%) at 2 years.[236]

More recently, O'Brien et al[237] reported that dose-intensive induction therapy with the hyperCVAD regimen induced CR rates of 84% in patients 60 years or older, with an improved 5-year OS rate (20% compared with 9% on regimens that were used before hyperCVAD) and decreased incidence of disease resistance. However, this regimen was also associated with higher treatment-related mortality (10% vs 2%) during induction and significantly higher incidence of death (34% vs 7%; *P*<.001) from infections associated with myelosuppression among older patients.

Philadelphia-chromosome (Ph) is the most frequent cytogenetic abnormality in older patients with ALL. Ph-chromosome results from the reciprocal translocation t(9;22) that fuses the *BCR* gene on chromosome 22 and the *ABL* gene located on chromosome 9. BCR-ABL tyrosine kinase inhibitors (imatinib and dasatinib) in combination with steroids have been evaluated as induction therapy in older patients with Ph-positive ALL.[238,239] In a phase II study of older patients with Ph-positive ALL (n=30; ≥60 years), induction therapy with imatinib and steroids induced complete remissions and prolonged survival without additional chemotherapy.[238] Median survival from diagnosis was 20 months. In another phase II study (n=55; 12 patients were older than 60 years), induction therapy with dasatinib and steroids and intrathecal chemotherapy induced complete remission rates in all patients.[239] At 20 months, the OS and DFS rates were 69% and 51%, respectively. In a randomized trial of 55 older patients, induction therapy with imatinib alone resulted in a significantly higher complete remission rate (96% vs 50%; *P*=.001) with lower toxicity compared with induction chemotherapy.[240] Severe adverse events were significantly more frequent with induction chemotherapy (90% vs 39%; *P*=.005). The OS was not significantly different between the groups. The use of imatinib and steroids as consolidation therapy following induction chemotherapy has also resulted in improved outcomes (compared with historical controls) in older patients with Ph-positive ALL.[241]

Among patients with CD20-positive and Ph-negative ALL, the benefit of adding rituximab to chemotherapy has been confined only to younger patients. In a study of 282 adolescents and patients with CD20-positive and Ph-negative ALL treated with a modified hyperCVAD and rituximab, the 3-year complete remission duration was 67% for younger patients compared with 45% for patients 60 years or older.[242] The 3-year OS rates were 78% and 45%, respectively.

AML: AML in older patients is associated with a poor prognosis. Increasing age, FLT3 internal tandem duplications, unfavorable cytogenetics, increasing white blood cell count, poorer performance status, and the presence of secondary AML are considered poor prognostic indicators in this group of patients.[243,244] A retrospective analysis of 968 patients with AML showed a marked increase in the proportion of patients with unfavorable cytogenetics (35% in patients <56 years to 51% in patients >75 years), prevalence of multidrug resistance (33% in patients <56 years compared with 57% in patients >75 years), and treatment-related mortality (especially in patients with poor performance status) within 30 days after induction therapy (82% among patients >75 years).[245]

In patients 60 years or older, although anthracycline-based induction chemotherapy regimens have resulted in CR rates ranging from 39% to 63%, median OS and DFS have remained poor (7–12 months).[246] Despite these poor outcomes, standard intensive treatment has been shown to improve early death and long-term survival rates compared with palliative treatment in most patients with AML up to 75 to 80 years of age.[247,248]

Induction chemotherapy should be considered for older patients with good performance status and no comorbidities. The optimal chemotherapy regimen is unknown. In a randomized trial (1314 patients older than 56 years) that compared 3 different induction regimens, DAT (daunorubicin, cytarabine, and thioguanine), ADE (cytarabine, daunorubicin and etoposide), and MAC (mitoxantrone and cytarabine), the remission rates in the DAT arm

were significantly better than in the ADE (62% vs 50%; *P*=.002) or MAC (62% vs 55%; *P*=.04) arms, but there were no differences in the 5-year OS rates between the 3 regimens (2% vs 8% vs 10%, respectively).[249] The remission or survival rates were also not improved by the addition of granulocyte colony-stimulating factor. In another study of 362 older patients with previously untreated AML (139 patients ≥70 years of age) randomized to receive daunorubicin, idarubicin, or mitoxantrone with a standard dose of cytarabine as induction therapy, no difference in efficacy was seen among the 3 regimens in terms of CR rate, OS, and DFS.[250] Conversely, an exploratory analysis of a randomized phase III trial that compared induction chemotherapy with mitoxantrone and etoposide (ME) versus daunorubicin and cytarabine (AD) showed that the use of etoposide with an anthracycline resulted in poor survival rates (11% and 19%, respectively, for ME and AD regimens) in patients with untreated AML older than 55 years of age, although no significant difference in CR rate was seen between the 2 regimens (34% and 43%, respectively, for patients treated with ME and AD). These findings suggest that cytarabine should be used in combination with an anthracycline for patients who are considered candidates for induction chemotherapy.[251]

Induction therapy with intensified anthracycline doses and cytarabine has not been consistently associated with improved outcomes in older patients.[252–256] For example, the LRF AML14 trial did not show any difference in CR rate or OS for patients treated with daunorubicin (50 vs 35 mg/m^2) and cytarabine (200 vs 400 mg/m^2) at 2 different dose levels.[253] In contrast to these findings, Lowenberg et al[254] showed that, in patients older than 60 years, dose escalation of daunorubicin (90 mg/m^2) resulted in a higher response rate than the conventional dose (45 mg/m^2), without any additional toxic effects. The CR rate was 64% and 54%, respectively (*P*=.002) but there was no difference in OS rates. The subgroup analysis showed a potential benefit for dose escalation of daunorubicin in patients 60 to 65 years of age (especially those with core binding factor [CBF] AML) in terms of CR (51% in the conventional-dose group vs 73% in the escalated-dose group), the 2-year DFS (14% vs 29%, respectively), and 2-year OS rates (23% vs 38%, respectively). The results from Acute Leukemia French Association (ALFA) trials (ALFA-9801 and ALFA-9803) also showed that although the use of idarubicin in combination with cytarabine resulted in higher CR rates than daunorubicin, it did not translate into a benefit in OS.[252,255] In a more recent report, a combined analysis of these two trials showed that induction therapy with idarubicin was associated with a significantly higher cure rate than daunorubicin (16.6% and 9.8%, respectively; *P*=.018) in patients 50 years or older.[256] In addition to younger age and favorable-risk AML, idarubicin treatment was also identified as a predictor of higher cure rate in multivariate analysis (*P*=.04), although it did not have any influence on OS (*P*=.11).[256]

Standard induction chemotherapy is associated with a 10% to 20% risk of death in patients older than 56 years. Prediction tools are available to assist in counseling older patients regarding the safety and efficacy of standard induction chemotherapy. The probability of obtaining a CR and the risk of treatment-related mortality can be calculated using a Web-based tool: http://www.aml-score.org/.[257] In view of the seriousness of the complications of AML treatment, older patients with AML should be treated according to the NCCN Guidelines for AML in centers skilled in the management and supportive care of those patients (to view the most recent version of these guidelines, visit NCCN.org).

Multiple Myeloma: High-dose therapy followed by autologous stem cell transplantation (HDT/ASCT) is the initial treatment for younger patients. However, the role of this approach in older patients has not yet been established in randomized trials because most of these trials included patients younger than 65 years. There is also lack of consensus on what constitutes transplant eligibility in older patients. Recent reports (mostly from retrospective studies) suggest that ASCT may be beneficial for selected older patients with good performance status and no severe comorbidities.[258–260] Initial evaluation should determine whether the patient is a potential candidate for HDT/ASCT. An older patient's eligibility for transplant should be based on the assessment of their physiologic rather than chronologic age, with specific attention to comorbidities, functional status, and adequate cardiac, pulmonary, renal, and hepatic function. Melphalan-based chemotherapy should be avoided in transplant candidates. Early referral to a transplant physician should be considered if uncertain whether the patient is transplant-eligible before exposure to alkylating agents.

Immunomodulator-Based Combination Therapy: In randomized studies, the addition of thalidomide to the combination of melphalan and prednisone (MP) was associated with significantly superior response rates, progression-free survival (PFS), time-to-treatment progression, and RFS in older patients with newly diagnosed multiple myeloma.[261–268] However, OS benefit was reported only in 2 of these studies. In the IFM 99-06 trial, which compared melphalan, prednisone, and thalidomide (MPT); MP; and reduced-intensity ASCT; median OS was 51.6, 33.2, and 38.3 months, respectively. The MPT regimen was associated with a significantly better OS than the MP regimen (P=.0006) and reduced-intensity ASCT (P=.027).[263] In the IFM 01/01 trial, median OS was 44 and 29 months, respectively (P=.028), for older patients (≥75 years) treated with MPT and MP.[264] MPT was associated with significant toxicity (constipation, fatigue, deep vein thrombosis [DVT], neuropathy, cytopenias, and infection).[268]

In a double-blind, multicenter, randomized study, induction therapy with melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged PFS in patients 65 years or older with newly diagnosed multiple myeloma that were ineligible for HDT/ASCT.[269] At a median follow-up of 30 months, the median PFS was significantly longer with MPR-R (31 months) than with MPR (14 months; P<.001) or MP (13 months; P<.001). The greatest PFS benefit was observed in patients 65 to 75 years of age.[269] MPR-R was also associated with higher response rate than MPR or MP (77%, 68%, and 50%, respectively). The results of a landmark analysis showed that MPR-R resulted in a 66% reduction in the rate of progression that was age-independent.

Bortezomib-Based Combination Therapy: Bortezomib-based combinations have been evaluated as initial therapy and maintenance therapy in older patients with untreated multiple myeloma. Induction therapy with bortezomib, melphalan, and prednisone (VMP) was superior to MP alone in patients (median age, 71 years) with newly diagnosed multiple myeloma who were ineligible for HDT/ASCT, and the survival benefit was seen across all age groups.[270,271] However, the rates of adverse events (peripheral neuropathy, cytopenias, and fatigue) were higher among patients in the VMP group than in the MP group. The subgroup analyses of the VISTA trial showed that VMP resulted in longer OS among patients younger than 75 years compared with those 75 years or older (3-year OS rates were 74.1% and 55.5%, respectively; P= .011).[271]

In the Spanish randomized trial that evaluated induction therapy with VMP or bortezomib, thalidomide, and prednisone (VTP) followed by maintenance therapy with bortezomib with thalidomide or prednisone in 260 older patients, VTP and VMP resulted in similar response rates (partial response rates were 81% and 80%, respectively) and OS, with different side-effect profiles in the induction phase.[272] Incidences of infection were higher in the VMP group and VTP was associated with higher incidences of cardiac events. In the maintenance setting, CR rates were higher with bortezomib and thalidomide (46%) compared with bortezomib and prednisone (39%).[272] In the updated report, the median PFS and the 5-year OS rate were also superior for bortezomib and thalidomide (39 months and 69%, respectively) compared with bortezomib and prednisone (32 months and 50%, respectively), but the differences were not statistically significant.[273] The achievement of CR was associated with a significantly longer PFS (P<.001) and 5-year OS (P<.001). However, peripheral neuropathy was higher with bortezomib and thalidomide (9%) compared with bortezomib and prednisone (3%).

In another phase III study, the 4-drug combination of bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) was associated with higher response rates and PFS compared with VMP alone but did not result in an improvement in OS.[274] The 3-year OS rates were 89% and 87%, respectively, for VMPT followed by VT and with VMP (P=.77). VMPT followed by VT was also associated with higher grade 3 or 4 toxicities (neutropenia and cardiologic and thromboembolic events). An updated analysis of this study (with a median follow-up of 47.2 months) showed that the VMPT-VT regimen significantly prolonged OS compared with VMP, especially in patients younger than 75 years (5-year OS rates were 67.8% and 49.9%, respectively; P=.01).[275] The VMPT-VT regimen also reduced the risk of death by 37% in patients 67 to 75 years of age.

In a phase II study, a sequential approach incorporating bortezomib-based induction therapy (bortezomib, doxorubicin, and dexamethasone) and ASCT

followed by maintenance therapy with lenalidomide improved overall response rates in older patients with newly diagnosed multiple myeloma. These findings have to be confirmed in randomized studies.[276]

Dexamethasone-Based Combination Therapy: Dexamethasone-based regimens are associated with increased mortality and severe hematologic toxicities compared with MP in older patients with newly diagnosed multiple myeloma who are not eligible for HDT/ASCT.[277,278] In a large randomized trial (IFM 95-01) comparing MP with dexamethasone-based regimens (dexamethasone alone or in combination with melphalan or interferon), although no difference was seen in OS among the 4 treatment groups, the response rate was significantly higher in patients receiving dexamethasone and melphalan. The PFS was significantly better for patients receiving MP and melphalan and dexamethasone; however, the toxicities associated with dexamethasone-based regimens (severe pyogenic infections in the melphalan-dexamethasone arm; hemorrhage, severe diabetes, and gastrointestinal and psychiatric complications in the dexamethasone arms) were significantly higher than with MP.[277]

The results of a recent randomized trial suggest the low-dose dexamethasone used in combination with lenalidomide is associated with better short-term OS and lower toxicity than high-dose dexamethasone and lenalidomide in patients with newly diagnosed myeloma.[278] DVT, infection including pneumonia, and fatigue were the most common grade 3 or 4 toxicities.

Deep Vein Thrombosis Prophylaxis: The incidence of venous and arterial thrombosis increases with the use of thalidomide or lenalidomide in combination with chemotherapy or dexamethasone. In a phase III randomized trial, aspirin and fixed low-dose warfarin showed similar safety and efficacy in reducing thromboembolic complications compared with low-molecular-weight heparin (LMWH) in patients with myeloma treated with thalidomide-based regimen, whereas in older patients LMWH was more effective than warfarin.[279] DVT prophylaxis with LMWH is recommended for older patients receiving regimens containing thalidomide or lenalidomide.

Myelodysplastic Syndromes: Myelodysplastic syndromes (MDS) are a diverse group of clonal hematologic disorders characterized by ineffective hematopoiesis subsequently leading to cytopenias and potential transformation to AML. In randomized phase III trials, DNA methyl transferase inhibitors such as azacitidine and decitabine have been shown to improve quality of life by decreasing the risk of AML transformation as well as transfusion dependence compared with conventional regimens or best supportive care in patients with high-risk MDS.[280–284]

The subgroup analysis of the AZA-001 trial demonstrated that azacitidine significantly improved OS compared with conventional care, with no increased risk of toxicity in older patients (≥75 years) with intermediate- or high-risk MDS.[285] The 2-year OS rates were 55% and 15%, respectively ($P<.001$). In a study of 282 patients with high-risk MDS, Itzykson et al[286] identified previous treatment with low-dose cytosine arabinoside, bone marrow blasts greater than 15%, and abnormal or complex karyotype as predictors of lower response rates; performance status 2 or greater, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion dependency 4 units/8 weeks or more were independent predictors of poorer OS. For patients with higher-risk MDS, azacytidine is given 7 days in a row. This schedule may be challenging for older patients due to logistic or transportation problems. In a phase II study, azacytidine schedule of 5-2-2 (5 days on, 2 days off, 2 days on) did not seem to negatively impact the response rate or duration of response in patients 65 years or older.[287]

A recent report from the Spanish Registry of MDS also demonstrated the equal efficacy of 3 different schedules of azacytidine (5-0-0, 5-2-2, and 7 days) in older patients (107 patients; ≥75 years) with low-intermediate risk and intermediate high-risk MDS. Transfusion independence was achieved in 40% of patients. With a median follow-up of 14 months, the median OS was 18 months and the probability of OS at 2 years was 34%.[288] A 5-day schedule is not recommended for patients with high-risk MDS. Azacitidine has also been shown to be a feasible and effective treatment for older patients (≥70 years) with low-risk MDS.[289,290]

In the 2 large studies that included predominantly older patients with low- and high-risk MDS, decitabine (5-day schedule given as 15 mg/m^2 every 8 hours for 3 days at a dose of 135 mg/m^2 per course) resulted in durable responses, hematologic, improvement and improved time to AML transformation or death.[282,291] However, in a phase III study of 232 older patients with intermediate- or high-risk MDS ineligible for intensive chemotherapy, decitabine resulted

in improvement in PFS (6.6 vs 3.0 months; *P*=.004) and AML transformation (22% vs 33% with best supportive care), but no significant difference was seen in OS (10.1 vs 8.5 months; *P*=.38) and AML-free survival (8.8 vs 6.1 months; *P*= .24) compared with best supportive care.[284] Longer duration of MDS and prior therapy were predictive factors for achieving CR, whereas abnormalities of chromosomes 5 or 7, older age, and prior therapy were adverse prognostic factors for survival.[283]

Lenalidomide has also been effective in transfusion-dependent patients with low-risk MDS with 5q deletions, resulting in the reduction of transfusion requirements and reversal cytologic and cytogenetic abnormalities.[292,293] The drug also has been shown to improve transfusion independence in patients with low-risk MDS without deletion 5q.[294] Although the median age of patients included in these studies is early 70s, few data are available regarding the risks and benefits at the extremes of age.

Summary

Cancer is the leading cause of death in women and men aged 60 to 79 years. The biologic characteristics of certain cancers are different in older patients compared with their younger counterparts, and older patients also have decreased tolerance to chemotherapy. Nevertheless, advanced age alone should not be the only criteria to preclude effective cancer treatment that could improve quality of life or lead to a survival benefit in older patients. Treatment should be individualized based on the nature of the disease, the physiologic status of the patient, and the patient's preferences.

Chronologic age is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. The best guide as to whether cancer treatment is appropriate may be provided by careful assessment of the older patient. CGA can be used to assess life expectancy and risk of morbidity from cancer in older patients. CGA in turn can enable physicians to develop a coordinated plan for cancer treatment as well as guide interventions tailored to the patient's problems.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
2. Altekruse SF, Kosary CL, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, avauilable at: http://seer.cancer.gov/csr/1975_2007/, Based on November 2009 SEER data submission, posted to the SEER web site, 2010.
3. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–2765.
4. Balducci L. Management of cancer in the elderly. Oncology (Williston Park) 2006;20:135–143.
5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004;22:4626–4631.
6. Saltzstein SL, Behling CA. 5- and 10-year survival in cancer patients aged 90 and older: a study of 37,318 patients from SEER. J Surg Oncol 2002;81:113–116; dicussion 117.
7. Extermann M. Management issues for elderly patients with breast cancer. Curr Treat Options Oncol 2004;5:161–169.
8. Chen H, Cantor A, Meyer J, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer 2003;97:1107–1114.
9. Christman K, Muss HB, Case LD, Stanley V. Chemotherapy of metastatic breast cancer in the elderly. The Piedmont Oncology Association experience [see comment]. JAMA 1992;268:57–62.
10. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091–1097.
11. Wedding U, Honecker F, Bokemeyer C, et al. Tolerance to chemotherapy in elderly patients with cancer. Cancer Control 2007;14:44–56.
12. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001;285:2750–2756.
13. Carey EC, Walter LC, Lindquist K, Covinsky KE. Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med 2004;19:1027–1033.
14. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801–808.
15. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58.
16. White DK, Neogi T, Nevitt MC, et al. Trajectories of gait speed predict mortality in well-functioning older adults: the Health, Aging and Body Composition Study. J Gerontol A Biol Sci Med Sci 2012;68:456–464.
17. Ostir GV, Berges I, Kuo YF, et al. Assessing gait speed in acutely ill older patients admitted to an acute care for elders hospital unit. Arch Intern Med 2012;172:353–358.
18. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824–1831.
19. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin 2010;60:120–132.
20. Rodin MB, Mohile SG. A practical approach to geriatric assessment in oncology. J Clin Oncol 2007;25:1936–1944.
21. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–919.

22. Lawton MP. Scales to measure competence in everyday activities. Psychopharmacol Bull 1988;24:609–614.
23. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005;16:1795–1800.
24. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865–6872.
25. Koroukian SM, Xu F, Bakaki PM, et al. Comorbidities, functional limitations, and geriatric syndromes in relation to treatment and survival patterns among elders with colorectal cancer. J Gerontol A Biol Sci Med Sci 2010;65:322–329.
26. Winkelmann N, Petersen I, Kiehntopf M, et al. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. J Cancer Res Clin Oncol 2011;137:733–738.
27. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people—results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675–1680.
28. Klepin HD, Geiger AM, Tooze JA, et al. Physical performance and subsequent disability and survival in older adults with malignancy: results from the health, aging and body composition study. J Am Geriatr Soc 2010;58:76–82.
29. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–148.
30. Pondal M, del Ser T. Normative data and determinants for the timed "up and go" test in a population-based sample of elderly individuals without gait disturbances. J Geriatr Phys Ther 2008;31:57–63.
31. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896–903.
32. Overcash JA, Rivera HR, Jr. Physical performance evaluation of older cancer patients: a preliminary study. Crit Rev Oncol Hematol 2008;68:233–241.
33. Extermann M. Interaction between comorbidity and cancer. Cancer Control 2007;14:13–22.
34. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clin Oncol 2010;28:4086–4093.
35. Nanda A, Chen MH, Braccioforte MH, et al. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009;302:866–873.
36. Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol 2003;21:433–440.
37. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 2009;27:2170–2176.
38. Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291:2441–2447.
39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
40. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622–626.
41. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 1981;36:428–434.
42. Breccia M, Latagliata R, Stagno F, et al. Charlson comorbidity index and adult comorbidity evaluation-27 scores might predict treatment compliance and development of pleural effusions in elderly patients with chronic myeloid leukemia treated with second-line dasatinib. Haematologica 2011;96:1457–1461.
43. Sanabria A, Carvalho AL, Melo RL, et al. Predictive factors for complications in elderly patients who underwent head and neck oncologic surgery. Head Neck 2008;30:170–177.
44. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000;18:2529–2536.
45. Hurria A, Brogan K, Panageas KS, et al. Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2005;92:151–156.
46. Fader AN, von Gruenigen V, Gibbons H, et al. Improved tolerance of primary chemotherapy with reduced-dose carboplatin and paclitaxel in elderly ovarian cancer patients. Gynecol Oncol 2008;109:33–38.
47. Gronberg BH, Sundstrom S, Kaasa S, et al. Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy. Eur J Cancer 2010;46:2225–2234.
48. Ngeow J, Leong SS, Gao F, et al. Impact of comorbidities on clinical outcomes in non-small cell lung cancer patients who are elderly and/or have poor performance status. Crit Rev Oncol Hematol 2010;76:53–60.
49. Sanabria A, Carvalho AL, Vartanian JG, et al. Comorbidity is a prognostic factor in elderly patients with head and neck cancer. Ann Surg Oncol 2007;14:1449–1457.
50. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in older adults with cancer. Oncologist 2010;15:507–522.
51. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. J Clin Pharm Ther 2007;32:169–175.
52. Puts MT, Costa-Lima B, Monette J, et al. Medication problems in older, newly diagnosed cancer patients in Canada: How common are they? A prospective pilot study. Drugs Aging 2009;26:519–536.
53. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. Lancet Oncol 2011;12:1249–1257.
54. Riechelmann RP, Saad ED. A systematic review on drug interactions in oncology. Cancer Invest 2006;24:704–712.
55. Riechelmann RP, Tannock IF, Wang L, et al. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst 2007;99:592–600.
56. Riechelmann RP, Zimmermann C, Chin SN, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage 2008;35:535–543.

57. Tam-McDevitt J. Polypharmacy, aging, and cancer. Oncology (Williston Park) 2008;22:1052–1055, discussion 1055, 1058, 1060.

58. Popa M, Wallace K, Brunello A, Extermann M. The impact of polypharmacy on toxicity from chemotherapy in elderly patients: focus on cytochrome P-450 inhibition and protein binding effects [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 9505.

59. Steinman MA, Seth Landefeld C, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006;54:1516–1523.

60. Currow DC, Stevenson JP, Abernethy AP, et al. Prescribing in palliative care as death approaches. J Am Geriatr Soc 2007;55:590–595.

61. Maggiore RJ, Gross CP, Hardt M, et al. Polypharmacy, potentially inappropriate medications, and chemotherapy-related adverse events among older adults with cancer. J Clin Oncol 2011;29:e19501.

62. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997;157:1531–1536.

63. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–2724.

64. Flood KL, Carroll MB, Le CV, Brown CJ. Polypharmacy in hospitalized older adult cancer patients: experience from a prospective, observational study of an oncology-acute care for elders unit. Am J Geriatr Pharmacother 2009;7:151–158.

65. Lichtman SM, Boparai MK. Geriatric medication management: Evaluation of pharmacist interventions and potentially inappropriate medication (PIM) use in older (>=65 years) cancer patients. J Clin Oncol 2009;27:9507.

66. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616–631.

67. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992;45:1045–1051.

68. Samsa GP, Hanlon JT, Schmader KE, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol 1994;47:891–896.

69. Schmader K, Hanlon JT, Weinberger M, et al. Appropriateness of medication prescribing in ambulatory elderly patients. J Am Geriatr Soc 1994;42:1241–1247.

70. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. Ann Pharmacother 2003;37:40–46.

71. Hanlon JT, Artz MB, Pieper CF, et al. Inappropriate medication use among frail elderly inpatients. Ann Pharmacother 2004;38:9–14.

72. Gallagher P, Baeyens JP, Topinkova E, et al. Inter-rater reliability of STOPP (screening tool of older persons' prescriptions) and START (screening tool to alert doctors to right treatment) criteria amongst physicians in six European countries. Age Ageing 2009;38:603–606.

73. Gallagher P, O'Mahony D. STOPP (screening tool of older persons' potentially inappropriate prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673–679.

74. Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007;36:632–638.

75. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther 2011;89:845–854.

76. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med 2002;18:737–757.

77. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116–122.

78. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366–372.

79. Bjorkman MP, Sorva AJ, Risteli J, Tilvis RS. Low parathyroid hormone levels in bedridden geriatric patients with vitamin D deficiency. J Am Geriatr Soc 2009;57:1045–1050.

80. Stilley CS, Bender CM, Dunbar-Jacob J, et al. The impact of cognitive function on medication management: three studies. Health Psychol 2010;29:50–55.

81. Extermann M. Older patients, cognitive impairment, and cancer: an increasingly frequent triad. J Natl Compr Canc Netw 2005;3:593–596.

82. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333–1341.

83. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc 2011;59:1477–1483.

84. Pasina L, Djade CD, Lucca U, et al. Association of anticholinergic burden with cognitive and functional status in a cohort of hospitalized elderly: comparison of the anticholinergic cognitive burden scale and anticholinergic risk scale: results from the REPOSI study. Drugs Aging 2013;30:103–112.

85. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943.

86. Kales HC, Valenstein M, Kim HM, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 2007;164:1568–1576; quiz 1623.

87. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168:1090–1096.

88. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med 2007;167:781–787.

89. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement 2013;9:141–150.

90. Seeman TE, Kaplan GA, Knudsen L, et al. Social network ties and mortality among the elderly in the Alameda County Study. Am J Epidemiol 1987;126:714–723.

91. Tomaka J, Thompson S, Palacios R. The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. J Aging Health 2006;18:359–384.

92. Kroenke CH, Kubzansky LD, Schernhammer ES, et al. Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol 2006;24:1105–1111.

93. Flood KL, Carroll MB, Le CV, et al. Geriatric syndromes in elderly patients admitted to an oncology-acute care for elders unit. J Clin Oncol 2006;24:2298–2303.

94. Naeim A, Reuben D. Geriatric syndromes and assessment in older cancer patients. Oncology (Williston Park) 2001;15:1567–1577.

95. Mohile SG, Fan L, Reeve E, et al. Association of cancer with geriatric syndromes in older Medicare beneficiaries. J Clin Oncol 2011;29:1458–1464.

96. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. J Am Geriatr Soc 2004;52:1681–1687.

97. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Arch Intern Med 2008;168:2033–2040.

98. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.

99. Katzman R, Brown T, Fuld P, et al. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry 1983;140:734–739.

100. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–935.

101. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–2391.

102. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699.

103. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. Support Care Cancer 2008;16:1273–1278.

104. Olson RA, Iverson GL, Carolan H, et al. Prospective comparison of two cognitive screening tests: diagnostic accuracy and correlation with community integration and quality of life. J Neurooncol 2011;105:337–344.

105. Njegovan V, Hing MM, Mitchell SL, Molnar FJ. The hierarchy of functional loss associated with cognitive decline in older persons. J Gerontol A Biol Sci Med Sci 2001;56:M638–643.

106. Borson S, Scanlan J, Brush M, et al. The Mini-Cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;15:1021–1027.

107. McCarten JR, Anderson P, Kuskowski MA, et al. Screening for cognitive impairment in an elderly veteran population: acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc 2011;59:309–313.

108. Ghosh A. Endocrine, metabolic, nutritional, and toxic disorders leading to dementia. Ann Indian Acad Neurol 2010;13:S63–68.

109. Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157–1165.

110. Bush SH, Bruera E. The assessment and management of delirium in cancer patients. Oncologist 2009;14:1039–1049.

111. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.

112. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 2008;56:823–830.

113. Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: assessing delirium in advanced cancer. Cancer 2000;88:2859–2867.

114. Gaudreau JD, Gagnon P, Harel F, et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005;29:368–375.

115. Inouye SK, Bogardus ST Jr, Baker DI, et al. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. J Am Geriatr Soc 2000;48:1697–1706.

116. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–676.

117. Gaudreau JD, Gagnon P, Harel F, et al. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712–6718.

118. Gaudreau JD, Gagnon P, Roy MA, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. Cancer 2007;109:2365–2373.

119. Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg 2012;215:453–466.

120. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.

121. D'Ath P, Katona P, Mullan E, et al. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994;11:260–266.

122. Jongenelis K, Pot AM, Eisses AMH, et al. Diagnostic accuracy of the original 30-item and shortened versions of the Geriatric Depression Scale in nursing home patients. Int J Geriatr Psychiatry 2005;20:1067–1074.

123. Jacobsen PB. Assessment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004:93–97.

124. Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing fatigue and depression in patients with cancer. Semin Clin Neuropsychiatry 2003;8:229–240.

125. Respini D, Jacobsen PB, Thors C, et al. The prevalence and correlates of fatigue in older cancer patients. Crit Rev Oncol Hematol 2003;47:273–279.

126. Hurria A, Li D, Hansen K, et al. Distress in older patients with cancer. J Clin Oncol 2009;27:4346–4351.

127. Zabora J, BrintzenhofeSzoc K, Jacobsen P, et al. A new psychosocial screening instrument for use with cancer patients. Psychosomatics 2001;42:241–246.

128. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.

129. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol 2007;25:4670–4681.

130. Hoffman BM, Zevon MA, D'Arrigo MC, Cecchini TB. Screening for distress in cancer patients: the NCCN rapid-screening measure. Psychooncology 2004;13:792–799.

131. Jacobsen PB, Donovan KA, Trask PC, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer 2005;103:1494–1502.

132. Hamerman D. Toward an understanding of frailty. Ann Intern Med 1999;130:945–950.

133. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–156.

134. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5:224–237.

135. Tucci A, Ferrari S, Bottelli C, et al. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer 2009;115:4547–4553.

136. Kristjansson SR, Rønning B, Hurria A, et al. A comparison of two pre-operative frailty measures in older surgical cancer patients. J Geriatric Oncol 2012;3:1–7.

137. Rao A, Cohen HJ. Symptom management in the elderly cancer patient: fatigue, pain, and depression. J Natl Cancer Inst Monogr 2004:150–157.

138. Minton O, Strasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European Palliative Care Research Collaborative Computerized Symptom Assessment Data Set. J Pain Symptom Manage 2012;43:226–235.

139. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998;16:3412–3425.

140. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol 1997;34:4–12.

141. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. Oncol Nurs Forum 1999;26:1663–1671.

142. Hardy SE, Studenski SA. Fatigue and function over 3 years among older adults. J Gerontol A Biol Sci Med Sci 2008;63:1389–1392.

143. Luciani A, Jacobsen PB, Extermann M, et al. Fatigue and functional dependence in older cancer patients. Am J Clin Oncol 2008;31:424-430.

144. Rao SS. Prevention of falls in older patients. Am Fam Physician 2005;72:81–88.

145. Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls: a prospective study in a large community-dwelling elderly cohort. BMC Geriatr 2009;9:30.

146. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009;169:1952–1960.

147. Puts MT, Monette J, Girre V, et al. The fall rate of older community-dwelling cancer patients. Support Care Cancer 2013;21:775.

148. Stone CA, Lawlor PG, Savva GM, et al. Prospective study of falls and risk factors for falls in adults with advanced cancer. J Clin Oncol 2012;30:2128–2133.

149. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. Support Care Cancer 2012;20:583–589.

150. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc 2011;59:148–157.

151. Chang JT, Morton SC, Rubenstein LZ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. BMJ 2004;328:680–680.

152. Campbell AJ, Robertson MC. Rethinking individual and community fall prevention strategies: a meta-regression comparing single and multifactorial interventions. Age Ageing 2007;36:656–662.

153. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;9.

154. Province MA, Hadley EC, Hornbrook MC, et al. The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT Trials. Frailty and Injuries: Cooperative Studies of Intervention Techniques. JAMA 1995;273:1341–1347.

155. Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:2997–3006.

156. Salonoja M, Salminen M, Vahlberg T, et al. Withdrawal of psychotropic drugs decreases the risk of falls requiring treatment. Arch Gerontol Geriatr 2012;54:160–167.

157. Balducci L. Bone complications of cancer treatment in the elderly. Oncology (Williston Park) 2010;24:741–747.

158. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: bone health in cancer care. J Natl Compr Canc Netw 2009;7 Suppl 3:S1–S32; quiz S33–S35.

159. Ingram SS, Seo PH, Martell RE, et al. Comprehensive assessment of the elderly cancer patient: the feasibility of self-report methodology. J Clin Oncol 2002;20:770–775.

160. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002;20:494–502.

161. Clough-Gorr KM, Thwin SS, Stuck AE, Silliman RA. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer 2011;48:805–812.

162. Caillet P, Canoui-Poitrine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol 2011;29:3636–3642.

163. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 2012;30:1829–1834.

164. Aparicio T, Jouve JL, Teillet L, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III Study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. J Clin Oncol 2013;31:1464–1470.

165. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood 2013;121:4287–4294.

166. Spina M, Balzarotti M, Uziel L, et al. Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. Oncologist 2012;17:838–846.

167. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer 2005;104:1998–2005.

168. Hamaker ME, Jonker JM, de Rooij SE, et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012;13:e437–444.

169. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in Cooperative Group Clinical Cancer Trials: CALGB 360401. J Clin Oncol 2011:1290–1296.

170. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–3465.

171. Extermann M. Evaluation of the senior cancer patient: comprehensive geriatric assessment and screening tools for the elderly. In: Schrijvers D, Aapro M, Zakotnik B, et al, eds. Handbook of Cancer in the Senior Patient. New York, London: Informa Healthcare; 2010:13–21.

172. Overcash JA, Beckstead J, Moody L, et al. The abbreviated comprehensive geriatric assessment (aCGA) for use in the older cancer patient as a prescreen: scoring and interpretation. Crit Rev Oncol Hematol 2006;59:205–210.

173. Kellen E, Bulens P, Deckx L, et al. Identifying an accurate pre-screening tool in geriatric oncology. Crit Rev Oncol Hematol 2010;75:243-248.

174. Molina-Garrido MJ, Guillen-Ponce C. Comparison of two frailty screening tools in older women with early breast cancer. Crit Rev Oncol Hematol 2011;79:51–64.

175. Biganzoli L, Boni L, Becheri D, et al. Evaluation of the cardiovascular health study (CHS) instrument and the Vulnerable Elders Survey-13 (VES-13) in elderly cancer patients. Are we still missing the right screening tool? Ann Oncol 2013;24:494–500.

176. Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23:2166–2172.

177. Pottel L, Boterberg T, Pottel H, et al. Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo)therapy. J Geriatric Oncol 2012;3:24–32.

178. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol 2013;24:1306–1312.

179. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001;49:1691–1699.

180. Mohile SG, Bylow K, Dale W, et al. A pilot study of the vulnerable elders survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. Cancer 2007;109:802–810.

181. Luciani A, Ascione G, Bertuzzi C, et al. Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and vulnerable elders survey-13. J Clin Oncol 2010;28:2046–2050.

182. Owusu C, Koroukian SM, Schluchter M, et al. Screening older cancer patients for a Comprehensive Geriatric Assessment: a comparison of three instruments. J Geriatr Oncol 2011;2:121–129.

183. Lachs MS, Feinstein AR, Cooney LM, et al. A simple procedure for general screening for functional disability in elderly patients. Ann Intern Med 1990;112:699–706.

184. Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? JAMA 2011;306:420–427.

185. Harrington SE, Smith TJ. The role of chemotherapy at the end of life: "when is enough, enough?". JAMA 2008;299:2667–2678.

186. Ramesh H, Pope D, Gennari R, Audisio R. Optimising surgical management of elderly cancer patients. World J Surg Oncol 2005;3:17.

187. Audisio RA, Bozzetti F, Gennari R, et al. The surgical management of elderly cancer patients; recommendations of the SIOG surgical task force. Eur J Cancer 2004;40:926–938.

188. Audisio RA, Ramesh H, Longo WE, et al. Preoperative assessment of surgical risk in oncogeriatric patients. Oncologist 2005;10:262–268.

189. Pope D, Ramesh H, Gennari R, et al. Pre-operative assessment of cancer in the elderly (PACE): a comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery. Surg Oncol 2006;15:189–197.

190. Audisio RA, Pope D, Ramesh HS, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008;65:156–163.

191. Robinson TN, Raeburn CD, Tran ZV, et al. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg 2009;249:173–178.

192. Robinson TN, Wu DS, Pointer LF, et al. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg 2012;215:12–17.

193. National Institute for Health and Care Excellence. Delirium: diagnosis, prevention and management. NICE clinical guideline 103; 2010. Available at: http://publications.nice.org.uk/delirium-cg103. Accessed December 23, 2013.

194. Zachariah B, Balducci L. Radiation therapy of the older patient. Hematol Oncol Clin North Am 2000;14:131–167.

195. Donato V, Valeriani M, Zurlo A. Short course radiation therapy for elderly cancer patients. Evidences from the literature review. Crit Rev Oncol Hematol 2003;45:305–311.

196. Mitsuhashi N, Hayakawa K, Yamakawa M, et al. Cancer in patients aged 90 years or older: radiation therapy. Radiology 1999;211:829–833.

197. Wasil T, Lichtman SM, Gupta V, Rush S. Radiation therapy in cancer patients 80 years of age and older. Am J Clin Oncol 2000;23:526–530.

198. Zachariah B, Balducci L, Venkattaramanabalaji GV, et al. Radiotherapy for cancer patients aged 80 and older: a study of effectiveness and side effects. Int J Radiat Oncol Biol Phys 1997;39:1125–1129.

199. Gelman RS, Taylor SG. Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trends in toxicity by using doses based on creatinine clearance. J Clin Oncol 1984;2:1404–1413.

200. Ibrahim NK, Frye DK, Buzdar AU, et al. Doxorubicin-based chemotherapy in elderly patients with metastatic breast cancer. Tolerance and outcome. Arch Intern Med 1996;156:882–888.

201. Giovanazzi-Bannon S, Rademaker A, Lai G, Benson AB. Treatment tolerance of elderly cancer patients entered onto

phase II clinical trials: an Illinois Cancer Center study. J Clin Oncol 1994;12:2447–2452.

202. Newcomb PA, Carbone PP. Cancer treatment and age: patient perspectives. J Natl Cancer Inst 1993;85:1580–1584.

203. Lichtman SM, Wildiers H, Chatelut E, et al. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients--an analysis of the medical literature. J Clin Oncol 2007;25:1832–1843.

204. Hurria A, Lichtman SM. Clinical pharmacology of cancer therapies in older adults. Br J Cancer 2008;98:517–522.

205. Extermann M, Bonetti M, Sledge GW, et al. MAX2—a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer 2004;40:1193–1198.

206. Shayne M, Crawford J, Dale DC, et al. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2006;100:255–262.

207. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2012;118:3377–3386.

208. Jelliffe RW, Jelliffe SM. Estimation of creatinine clearance from changing serum-creatinine levels. Lancet 1971;2:710.

209. Agostara B, Carruba G, Usset A. The management of cancer in the elderly: targeted therapies in oncology. Immun Ageing 2008;5:16.

210. Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227–242.

211. Widakowich C, de Castro G Jr, de Azambuja E, et al. Review: side effects of approved molecular targeted therapies in solid cancers. Oncologist 2007;12:1443–1455.

212. Floyd JD, Nguyen DT, Lobins RL, et al. Cardiotoxicity of cancer therapy. J Clin Oncol 2005;23:7685–7696.

213. Boehm S, Rothermundt C, Hess D, Joerger M. Antiangiogenic drugs in oncology: a focus on drug safety and the elderly—a mini-review. Gerontology 2010;56:303–309.

214. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231–2247.

215. Abdullah SE, Haigentz M Jr, Piperdi B. Dermatologic toxicities from monoclonal antibodies and tyrosine kinase inhibitors against EGFR: pathophysiology and management. Chemother Res Pract 2012;2012:351210.

216. Maloney KW, Kagan SH. Adherence and oral agents with older patients. Semin Oncol Nurs 2011;27:154–160.

217. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010;28:4120–4128.

218. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. J Clin Oncol 2001;19:322–328.

219. Fink AK, Gurwitz J, Rakowski W, et al. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. J Clin Oncol 2004;22:3309–3315.

220. Lash TL, Fox MP, Westrup JL, et al. Adherence to tamoxifen over the five-year course. Breast Cancer Res Treat 2006;99:215–220.

221. Owusu C, Buist DS, Field TS, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 2008;26:549–555.

222. De Maio E, Gravina A, Pacilio C, et al. Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. BMC Cancer 2005;5:30.

223. Partridge AH, Archer L, Kornblith AB, et al. Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: adherence companion study 60104. J Clin Oncol 2010;28:2418–2422.

224. Barcenas CH, Zhang N, Zhao H, et al. Anthracycline regimen adherence in older patients with early breast cancer. Oncologist 2012;17:303–311.

225. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126:529–537.

226. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood 2009;113:5401–5411.

227. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 2010;28:2381–2388.

228. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood 2011;117:3733–3736.

229. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 2012;30:936–942.

230. Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. Clin Breast Cancer 2008;8:155–161.

231. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood 2007;109:3189–3197.

232. Marks DI, Paietta EM, Moorman AV, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). Blood 2009;114:5136–5145.

233. Taylor PR, Reid MM, Bown N, et al. Acute lymphoblastic leukemia in patients aged 60 years and over: a population-based study of incidence and outcome. Blood 1992;80:1813–1817.

234. Kantarjian HM, O'Brien S, Smith T, et al. Acute lymphocytic leukaemia in the elderly: characteristics and outcome with the vincristine-adriamycin-dexamethasone (VAD) regimen. Br J Haematol 1994;88:94–100.

235. Delannoy A, Sebban C, Cony-Makhoul P, et al. Age-adapted induction treatment of acute lymphoblastic leukemia in the elderly and assessment of maintenance with interferon combined with chemotherapy. A multicentric prospective study in forty patients. French Group for Treatment of Adult Acute Lymphoblastic Leukemia. Leukemia 1997;11:1429–1434.

236. Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. Haematologica 2011;96:245–252.

237. O'Brien S, Thomas DA, Ravandi F, et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. Cancer 2008;113:2097–2101.

238. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676–3678.

239. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521–6528.

240. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer 2007;109:2068–2076.

241. Delannoy A, Delabesse E, Lheritier V, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. Leukemia 2006;20:1526–1532.

242. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol 2010;28:3880–3889.

243. Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. Br J Haematol 2009;145:598–605.

244. Stirewalt DL, Kopecky KJ, Meshinchi S, et al. Size of FLT3 internal tandem duplication has prognostic significance in patients with acute myeloid leukemia. Blood 2006;107:3724–3726.

245. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood 2006;107:3481–3485.

246. Hiddemann W, Kern W, Schoch C, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol 1999;17:3569–3576.

247. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 2009;113:4179–4187.

248. Juliusson G. Older patients with acute myeloid leukemia benefit from intensive chemotherapy: an update from the Swedish Acute Leukemia Registry. Clin Lymphoma Myeloma Leuk 2011;11(Suppl 1):S54–59.

249. Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302–1311.

250. Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 2004;103:479–485.

251. Anderson JE, Kopecky KJ, Willman CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood 2002;100:3869–3876.

252. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109:5129–5135.

253. Burnett AK, Milligan D, Goldstone A, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. Br J Haematol 2009;145:318–332.

254. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235–1248.

255. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808–814.

256. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. J Clin Oncol 2013;31:321–327.

257. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 2010;376:2000–2008.

258. Bashir Q, Shah N, Parmar S, et al. Feasibility of autologous hematopoietic stem cell transplant in patients aged >/=70 years with multiple myeloma. Leuk Lymphoma 2012;53:118–122.

259. El Cheikh J, Kfoury E, Calmels B, et al. Age at transplantation and outcome after autologous stem cell transplantation in elderly patients with multiple myeloma. Hematol Oncol Stem Cell Ther 2011;4:30–36.

260. Muta T, Miyamoto T, Fujisaki T, et al. Evaluation of the feasibility and efficacy of autologous stem cell transplantation in elderly patients with multiple myeloma. Intern Med 2013;52:63–70.

261. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825–831.

262. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 2008;112:3107–3114.

263. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209–1218.

264. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664–3670.

265. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405–1412.

266. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28:3160–3166.

267. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16–22.

268. Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide

for elderly and/or transplant-ineligible patients with multiple myeloma: a meta-analysis. Leukemia 2011;25:1523–1524.

269. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759–1769.

270. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–917.

271. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259–2266.

272. Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010;11:934–941.

273. Mateos MV, Oriol A, Martinez-Lopez J, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 2012;120:2581–2588.

274. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101–5109.

275. Palumbo A, Bringhen S, Rossi D, et al. Overall survival benefit for bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients [abstract]. J Clin Oncol 2012;120:Abstract 200.

276. Palumbo A, Gay F, Falco P, et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. J Clin Oncol 2010;28:800–807.

277. Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 2006;107:1292–1298.

278. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29–37.

279. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011;29:986–993.

280. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002;20:2429–2440.

281. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223–232.

282. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 2006;106:1794–1803.

283. Kantarjian HM, O'Brien S, Shan J, et al. Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome. Cancer 2007;109:265–273.

284. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011;29:1987–1996.

285. Seymour JF, Fenaux P, Silverman LR, et al. Effects of azacitidine compared with conventional care regimens in elderly (≥ 75 years) patients with higher-risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2010;76:218–227.

286. Itzykson R, Thepot S, Quesnel B, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood 2011;117:403–411.

287. Breccia M, Loglisci G, Salaroli A, et al. 5-azacitidine efficacy and safety in patients aged >65 years with myelodysplastic syndromes outside clinical trials. Leuk Lymphoma 2012;53:1558–1560.

288. Xicoy B, Jimenez MJ, Garcia O, et al. Results of treatment with azacitidine in patients aged ≥ 75 years included in the Spanish Registry of Myelodysplastic Syndromes. Leuk Lymphoma 2013.

289. Musto P, Maurillo L, Spagnoli A, et al. Azacitidine for the treatment of lower risk myelodysplastic syndromes: a retrospective study of 74 patients enrolled in an Italian named patient program. Cancer 2010;116:1485–1494.

290. Komrokji R, List A, M Sekeres M, et al. Azacitidine treatment patterns, hematologic improvement, and tolerability in a large group of elderly patients with myelodysplastic syndromes in the avida registry treated in a community setting [abstract]. Haematologica 2010;95(Suppl 2):220 (Abstract 538).

291. Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol 2009;27:3842–3848.

292. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456–1465.

293. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. Blood 2011;118:3765–3776.

294. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood 2008;111:86–93.

Individual Disclosures for the NCCN Senior Adult Oncology Panel Members

Panel Member	Clinical Research Support/ Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Sarah L. Blair, MD	None	None	None	None	7/22/13
Ilene S. Browner, MD	None	None	None	None	6/11/13
Harvey Jay Cohen, MD	None	None	None	None	6/7/13
Mollie deShazo, MD	None	None	None	None	8/19/12
Efrat Dotan, MD	Biocompatibles	None	None	None	5/23/13
Barish H. Edil, MD					**Pending**
Martine Extermann, MD, PhD	None	None	None	None	5/24/13
Apar Kishor P. Ganti, MD	Pfizer Inc.	Boehringer Ingelheim GmbH	None	None	5/25/13
Holly M. Holmes, MD	None	None	None	None	5/27/13
Arti Hurria, MD	Celgene Corporation; and GlaxoSmithKline	GTx; and Seattle Genetics	None	None	11/24/13
Reshma Jagsi, MD, PhD	Abbott Laboratories; and University of Michigan	Eviti	None	None	11/25/13
Mohana B. Karlekar, MD	None	hospice compassus	None	None	11/24/13
Nancy L. Keating, MD, MPH	None	None	None	None	11/22/13
Beatriz Korc-Grodzicki, MD, PhD	None	None	None	None	5/28/13
June M. McKoy, MD, JD, MBA	None	None	None	None	6/11/13
Bruno C. Medeiros, MD	Celgene Corporation; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Celator; and Roche Laboratories, Inc.	Agios	None	None	5/29/13
Ewa Mrozek, MD	None	None	None	None	11/24/13
Tracey O'Connor, MD	None	None	None	None	6/13/13
Hope S. Rugo, MD	None	None	None	None	10/14/13
Randall W. Rupper, MD, MPH	None	None	None	None	10/24/12
Rebecca A. Silliman, MD, PhD, MPH	None	None	None	None	4/9/13
Derek L. Stirewalt, MD	None	None	None	None	10/11/12
William P. Tew, MD	None	None	None	None	4/2/13
Louise C. Walter, MD	None	None	None	None	4/2/13
Alva B. Weir III, MD	None	None	None	None	3/29/13
Tanya Wildes, MD	None	None	None	None	4/10/13

The NCCN Guidelines Staff have no conflicts to disclose.