CE Focused Review

Hematopoietic Stem Cell Transplantation for Hematologic Malignancies in Older Adults: Geriatric Principles in the Transplant Clinic

Tanya M. Wildes, MD, MSCI[a]; Derek L. Stirewalt, MD[b]; Bruno Medeiros, MD[c]; and Arti Hurria, MD[d]

Abstract

Hematopoietic cell transplantation (HCT) provides a life-prolonging or potentially curative treatment option for patients with hematologic malignancies. Given the high transplant-related morbidity, these treatment strategies were initially restricted to younger patients, but are increasingly being used in older adults. The incidence of most hematologic malignancies increases with age; with the aging of the population, the number of potential older candidates for HCT increases. Autologous HCT (auto-HCT) in older patients may confer a slightly increased risk of specific toxicities (such as cardiac toxicities and mucositis) and have modestly lower effectiveness (in the case of lymphoma). However, auto-HCT remains a feasible, safe, and effective therapy for selected older adults with multiple myeloma and lymphoma. Similarly, allogeneic transplant (allo-HCT) is a potential therapeutic option for selected older adults, although fewer data exist on allo-HCT in older patients. Based on currently available data, age alone is not the best predictor of toxicity and outcomes; rather, the comorbidities and functional status of the older patient are likely better predictors of toxicity than chronologic age in both the autologous and allogeneic setting. A comprehensive geriatric assessment (CGA) in older adults being considered for either an auto-HCT or allo-HCT may identify additional problems or geriatric syndromes, which may not be detected during the standard pretransplant evaluation. Further research is needed to establish the utility of CGA in predicting toxicity and to evaluate the quality of survival in older adults undergoing HCT. (*J Natl Compr Canc Netw* 2014;12:128–136)

NCCN: Continuing Education

Accreditation Statement

This activity has been designated to meet the educational needs of physicians and nurses involved in the management of patients with cancer. There is no fee for this article. No commercial support was received for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians.

NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center`s Commission on Accreditation.

This activity is accredited for 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/37102;** and 4) view/print certificate.

Release date: January 23, 2014; Expiration date: January 23, 2015

Learning Objectives

Upon completion of this activity, participants will be able to:

- Identify the predictors of toxicities and outcomes in older patients undergoing of HCT
- Discuss the safety and efficacy of HCT in older patients with hematologic malignancies
- Summarize the role of CGA in the selection of patients for HCT

From [a]Washington University School of Medicine, St. Louis, Missouri; [b]Fred Hutchinson Cancer Research Center, Seattle, Washington; [c]Stanford University School of Medicine, Stanford, California; and [d]City of Hope Comprehensive Cancer Center, Duarte, California.

Submitted July 24, 2013; accepted for publication November 8, 2013.

Drs. Wildes, Stirewalt, and Medeiros have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Hurria has disclosed that she receives research support from Celgene Corporation and GlaxoSmithKline, and is a consultant for GTx, Inc. Dr. Wildes' research is supported by Grant Number 1K12CA167540 through the National Cancer Institute (NCI) at the National Institutes of Health (NIH) and Grant Number UL1 TR000448 through the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCI, NCATS or NIH.

Correspondence: Tanya M. Wildes, MD, MSCI, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8056, St Louis, MO 63110.
E-mail: twildes@dom.wustl.edu

EDITOR
Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*
Ms. Green has disclosed that she has no relevant financial relationships.

CE AUTHORS
Deborah J. Moonan, RN, BSN, Manager, CE Supporter Outreach
Ms. Moonan has disclosed the following relationship with commercial interests: AstraZeneca: Stockholder/Former Employee.

Ann Gianola, MA, Manager, Medical Education Accreditation and Grant Development
Ms. Gianola has disclosed the following relationship with commercial interests: Actelion: Grant/Research Support.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations
Ms. Gregory has disclosed that she has no relevant financial relationships.

The incidence of most hematologic malignancies increases with age.[1–3] With the aging of the population, a disproportionate increase in the number of older adults diagnosed with hematologic malignancies is looming.[4] Aging is associated with a greater prevalence of impaired functional status[3] and comorbid medical conditions.[5] However, the aging process is heterogeneous, and chronologic age alone does not adequately reflect the health status of an older individual.

Hematopoietic cell transplant (HCT) provides a potentially life-prolonging or curative option for many patients with hematologic malignancies, and with greater experience and improved supportive care, physicians are increasingly referring older adults for this procedure. The Center for International Blood and Marrow Transplant Research has recorded a significant increase in the number of older adults undergoing autologous (auto-HCT) or allogeneic transplant (allo-HCT). In 1994–1995, fewer than 1% of patients who underwent auto-HCTs were aged 70 years or older; in 2004–2005, this percentage increased to 5%.[6] The percentage of auto-HCTs performed in patients aged 60 to 69 increased even more precipitously during that period, from 6% to 25%. The same trend has been seen with allo-HCT: between 1994 and 2005, the number of patients older than 60 years who underwent allo-HCT increased 13-fold.[7]

This trend of increasing numbers of older adults undergoing HCT will likely continue, because of an increasing number of older patients being diagnosed with hematologic malignancies. Thus, a detailed examination of the evidence regarding the use of auto-HCT and allo-HCT in older adults is relevant and timely. This article discusses the available data regarding the feasibility, tolerability, toxicity, and effectiveness of auto-HCT and allo-HCT in older adults (Table 1), and reviews the role of comprehensive geriatric assessment (CGA), which can be used to globally evaluate the functional status, comorbidities, medications, cognition, nutritional status, psychological state, and social support of older adults who may be candidates for HCT. Finally, the limitations of the currently available data on HCT in older adults are described, and opportunities are identified for future research to fill in these knowledge gaps and improve the care of older adults with hematologic malignancies.

Auto-HCT

Auto-HCT may be used as part of initial therapy or after relapse in older adults with several hematologic malignancies. The available data on auto-HCT in older adults are limited; studies are largely retrospective and examine highly selected groups of patients. With these caveats in mind, stem cell mobilization, engraftment, tolerability, and efficacy among older adults undergoing auto-HCT appear overall to be similar to those among younger adults, with the exceptions that are discussed in this section.

Stem Cell Mobilization

Preclinical models confirm substantial changes in aged hematopoietic stem and progenitor cells, with reduced engraftment and homing function, altered cell-surface proteins and transcriptional activity, and accumulating DNA damage.[8] These changes may underlie clinical differences in hematopoietic cell mobilization between older and younger patients. Older patients with myeloma tend to mobilize fewer total progenitor or $CD34^+$ cells/kg, and require more apheresis procedures to collect adequate numbers of cells.[9] In a large cohort study of all patients with multiple myeloma undergoing mobilization, age was independently associated with poor collection (defined as $\leq 1 \times 10^6$ $CD34^+$ cells/kg/d), although 92% of older patients were able to collect adequate stem cells to proceed with a single auto-HCT.[10] Among older adults with lymphoma, stem cell harvest is feasible and as successful as in younger patients.[11,12] Plerixafor, the CXCR4 antagonist, provides a promising chemotherapy-free mobilization regimen that improves the rates of successful mobilization in older adults with myeloma and lymphoma over granulocyte colony-stimulating factor alone.[13]

Toxicity of Auto-HCT

Early restriction of the use of auto-HCT to younger adults undoubtedly stemmed from concerns about increased risk of toxicity for older patients. Several studies have now shown that selected older adults with myeloma have similar time to neutrophil or platelet engraftment as younger patients and can tolerate auto-HCT without a substantially increased risk of toxicity.[14–16] Nevertheless, some specific toxicities may occur with greater frequency among older patients with myeloma undergoing auto-HCT. For example, older adults may experience greater risk of cardiac toxicity (50% vs 10%; $P<.0001$),[17] arrhythmia (8% vs 0%; $P=.02$),[18] and oral/

Table 1 Summary Conclusions on Currently Available Data on Auto-HCT and Allo-HCT in Older Adults

Auto-HCT

- Few studies exist evaluating the efficacy of auto-HCT in patients older than 65 years; essentially no studies exist that evaluate auto-HCT in patients older than 75 years.
- Available data are primarily derived from retrospective studies of selected patients that may be subject to intrinsic biases associated with these analyses; most studies were confined to patients with multiple myeloma and/or lymphoma.
- Older adults are able to mobilize adequate numbers of stem cells for auto-HCT.
- Comorbidity risk factors associated with poor outcomes in younger adults are also informative for older adults.
- Conditioning regimens containing ablative total body irradiation are associated with a higher TRM for adults older than 65 years.
- Older adults may display a modestly higher risk for specific toxicities and TRM, but older adults tolerate the procedure reasonably well.
- Older adults with specific types of malignancies may have a slightly higher risk of relapse, but auto-HCT displays a similar effectiveness in older adults as in younger adults.
- Large prospective studies are needed to evaluate the efficacy of auto-HCT for adults older than 65 years.

Allo-HCT

- Retrospective studies suggest that selected older adults with MDS undergoing an allo-HCT experience no increase in TRM; data in patients older than 75 years are extremely limited.
- Among participants in a clinical trial of adults aged 60 to 75 years with acute myeloid leukemia, MDS, chronic lymphocytic leukemia, lymphoma, and multiple myeloma, age was not associated with nonrelapse mortality, progression-free survival, or overall survival; comorbidities were prognostic.

Abbreviations: allo-HCT, allogeneic hematopoietic cell transplant; auto-HCT, autologous hematopoietic cell transplant; MDS, myelodysplastic syndromes; TRM, treatment-related mortality.

gastrointestinal toxicity (45% vs 23%; *P*=.06)[16] after auto-HCT. However, these age-related increases in toxicities have not been reported across all studies, and, in one report, older adults actually had less nausea than their younger counterparts (5% vs 18%; *P*=.007).[17]

Similarly, among older adults with lymphoma who undergo auto-HCT, some complications, such as nausea, mucositis, cardiovascular events (eg, atrial fibrillation), and neurologic complications may be more frequent, however, not all studies have consistently shown an increased risk for these complications.[17,19–21] Infections, sinusoidal obstruction syndrome (formerly veno-occlusive disease), and pneumonitis, which were major concerns in earlier studies,[22–24] are not more frequent in recent studies of older patients with lymphoma.[17,19–21] Moreover, time to neutrophil engraftment, antibiotic use, and length of hospitalization are similar for younger and older patients undergoing auto-HCT for lymphoma.[17,19–21] One notable exception is platelet count recovery, which may be slightly delayed in older patients with lymphoma.[19,21]

Treatment-Related Mortality of Auto-HCT

Early studies suggested that older adults undergoing auto-HCT were at greater risk for transplant-related complications and treatment-related mortality (TRM).[22–24] Several large retrospective studies estimated the 1-year TRM for older patients (age ≥55 years) to be 25% to 38%.[22–24] However, these older studies frequently included patients who were conditioned with high-dose total body irradiation (TBI), which has been associated with TRM as high as 60% in older patients.[22] Moreover, the older studies did not examine the impact of comorbidities, rather than age, on TRM.

With the adoption of better supportive care and reduction in the use of TBI-based conditioning, TRM rates for older adults undergoing auto-HCT have substantially improved. Recent studies report 1-year TRM rates for older patients (age ≥55 years) of 4% to 12%, which are similar or slightly higher than those reported for younger patients.[17,19,20,25–29] In addition, the same risk factors associated with increased TRM in younger adults remain informative for older adults: poor performance status,[27,28] high comorbidity index,[19] multiple prior therapies,[27,29] and advanced or chemotherapy-resistant disease.[27,28] Subgroups of older patients may continue to have a modestly higher TRM than their younger counter-

parts. One study reported that older patients with advanced follicular or high-grade lymphoma had a significantly higher 5-year TRM than their younger counterparts (15% vs 9%), even after adjusting for other potential prognostic factors.[28] Thus, when considering the potential TRM for older adults, patients must be carefully evaluated to determine how medically fit they are to undergo auto-HCT.

The previously described studies were primarily retrospective in nature. In addition, the evaluated patients were relatively heterogeneous, including various types and stages of hematologic malignancies, and a variety of different conditioning regimens. Moreover, most analyses used age cutoffs between 55 and 60 years to denote "older" patients. Two relatively small retrospective studies described the feasibility of auto-HCT for patients with lymphoma aged 69 years and older,[30,31] which represents the age group frequently afflicted by this malignancy. For this patient population, the 1-year nonrelapse mortality (NRM) rate may be significantly higher than that in patients aged 65 to 69 years (35% vs 8%; *P*=.0017), with a higher proportion of deaths attributable to infection in the older group.[31] Certainly, the limited numbers of patients and retrospective nature of these analyses require cautious interpretation and may not be generalizable to other patients older than 69 years. Similarly, data on patients with multiple myeloma older than 70 years are sparse. In one series of 84 patients older than 70 years who underwent auto-HCT for myeloma, 42% of patients experienced grade III/IV toxicity; yet, the 100-day NRM rate was only 3%.[32]

Efficacy/Effectiveness of Auto-HCT

Studies on the effectiveness of auto-HCT in older adults have included patients harboring multiple different types of hematologic malignancies, making it difficult to precisely define clinical outcomes for any specific population of older patients. By far, auto-HCT has been used as a therapeutic option most frequently for older adults with either multiple myeloma or lymphoma. Therefore, this article reviews the effectiveness of this procedure separately for these 2 malignancies, with the realization that even within these 2 malignancies substantial heterogeneity remains.

Although randomized trials have established the efficacy of auto-HCT for multiple myeloma, these trials categorically excluded patients older than 65 years.[33,34] No randomized trials have examined the efficacy of auto-HCT with high-dose conditioning (ie, melphalan, 200 mg/m^2) versus conventional therapy in older adults. Several cohort studies, however, have compared the clinical outcomes for younger and older patients who underwent auto-HCT. In these studies, younger and older patients had similar response rates, progression-free survival (PFS)/time-to-progression (TTP), and overall survival (OS),[14,15,18,35] suggesting that auto-HCT may be a reasonable option for selected older adults with myeloma.

The effectiveness of auto-HCT compared with conventional or novel therapies for myeloma in older adults is also not clear. In a population-based registry study, adults aged 60 to 64 years who underwent auto-HCT had superior OS compared with patients of the same age who received only conventional chemotherapy; however, potentially confounding factors such as performance status and comorbidities were not taken into account.[36] Furthermore, the role of auto-HCT in the era of novel therapeutic agents, including the immunomodulatory agents and proteasome inhibitors, is uncertain. In a phase II trial of thalidomide, pegylated liposomal doxorubicin, and dexamethasone (ThaDD), patients ineligible for auto-HCT received 6 cycles of ThaDD plus maintenance thalidomide, whereas transplant-eligible patients older than 65 years received 4 cycles of ThaDD, followed by auto-HCT with melphalan conditioning. Although patients who underwent auto-HCT had a higher complete response rate (57% vs 24%; *P*=.023), no significant difference in PFS (32 vs 29 months; *P*=.73), TTP (32 vs 31 months; *P*=.96), or estimated 5-year OS rate (49% vs 46%; *P*=.40) between patients who underwent auto-HCT and those receiving thalidomide maintenance.[37] A phase III study randomized patients aged 65 to 75 years with newly diagnosed multiple myeloma to standard melphalan and prednisone (MP) versus MP with thalidomide (MPT) versus intermediate-dose melphalan (100 mg/m^2; MEL100) with auto-HCT.[38] In this vulnerable older population, the complete response rates (18% vs 13%) and very good partial response (VGPR) rates (43% vs 47%) were similar between MEL100 and MPT, with the MP group having significantly lower complete response (2%) and VGPR (7%) rates. However, the patients treated with MPT had an improved PFS compared with ei-

ther MEL100 (hazard ratio [HR], 0.54; $P<.001$) or MP (HR, 0.45; $P<.001$). Patients treated with MPT also demonstrated an improved OS compared with MP (HR, 0.56; $P=.002$) and MEL100 (HR, 0.60; $P=.009$). One potential limitation of this study was that the patients treated with auto-HCT received lower doses of melphalan conditioning (100 mg/m^2), which some consider intermediate-dose as opposed to high-dose therapy. Thus, the role of auto-HCT in older adults in the era of novel therapies remains an area of active investigation.

In the context of lymphoma, the response to auto-HCT remains dependent on the subtype and stage of lymphoma, which makes studies examining the effectiveness of auto-HCT among all subtypes of lymphoma difficult to interpret. Notwithstanding this limitation, several retrospective studies of older adults undergoing auto-HCT suggest that older adults may have a slightly increased risk of relapse, and modestly decreased OS, relapse-free survival (RFS), and/or PFS,[25,27,28] although these findings have not been demonstrated in all studies.[17,19,29] Two of the largest studies showed an increased relative risk of death for older patients after auto-HCT, which was approximately 1.3 to 1.5 that found in younger adults.[27,28] As with younger patients, adverse risk factors for OS, RFS, and PFS in older adults include poor performance status, multiple prior therapies, advanced or chemotherapy-resistant disease, high lactate dehydrogenase, and male gender.[19,25,27–29]

Allo-HCT

Allo-HCT is a potentially curative treatment for hematologic malignancies, preferentially recommended to patients with high-risk features after initial chemotherapy, or after relapse. However, the use of immunosuppressive therapy and risk of graft-versus-host disease leads to high rates of transplant-related mortality, especially in older adults.

Donor Selection

Donor selection is a critical element contributing to the success of allo-HCT. This is particular true in patients older than 50 to 55 years where an HLA-identical sibling is available to only 30% of the patients in need. In nearly half of cases, a matched sibling may not be available or eligible to serve as a donor.[39] For patients lacking a suitable family donor, matched unrelated donors provide an alternative option, and recent reports suggest that patients with HLA-matched related or unrelated donors have similar survival.[40] Umbilical cord blood or mismatched related (haploidentical) donors can also be used, but unlike allo-HCT from an unrelated donor, these can be associated with an increased risk of morbidity and mortality, especially in older individuals.[41] Finally, in patients older than 50 years, priority should be given to HLA-matched sibling donors, rather than younger HLA-matched unrelated donors, because the use of unrelated donors has been associated with worse relapse rates, NRM, and OS.[42]

Allo-HCT Conditioning

Historically, older patients (>50–55 years) with hematologic malignancies were ineligible to receive allo-HCT with myeloablative conditioning regimens. Thus, reports on the outcomes of these patients are scarce and representative of highly selected individuals.[43] The development of lower-intensity (reduced-intensity or nonmyeloablative) conditioning regimens allows allo-HCT to be performed in patients previously considered ineligible. Although most studies comparing the results of myeloablative with reduced-intensity conditioning are limited to patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), conditioning regimen intensity alone has not consistently been an independent predictor of worse outcomes.[44,45] Nonetheless, these results must be interpreted with caution, because they represent a highly selected cohort of patients, and age should only be one of many factors considered when deciding an optimal conditioning regimen for an older patient.

Toxicity of Allo-HCT in Older Adults

Although most patients older than 50 to 55 years are ineligible to receive allo-HCT with myeloablative regimens, chronologic age alone fails to reliably predict posttransplant toxicity. In a clinical trial of adults aged 60 to 75 years, age was not associated with hospitalizations, graft-versus-host disease, or NRM.[46] Several recent studies have confirmed that advanced age (even >70 years) is not associated with higher rates of relapse or NRM, or poorer survival.[47,48] Rather, comorbidity indices, such as the Pretransplantation Assessment of Mortality and the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), seem to better reflect the true biologic age and are better predictors of

NRM and survival.[49,50] The HCT-CI is an adaptation of the Charlson Comorbidity Index (CCI) for the transplant setting; it assigns weights to 19 chronic conditions according to their association with 1-year mortality. The HCT-CI is a powerful predictive tool for transplant-related toxicity and mortality in older adults with high-risk myeloid malignancies.[51–53]

Efficacy/Effectiveness of Allo-HCT

Three large retrospective analyses have recently addressed the efficacy of allo-HCT in older patients with AML and MDS.[44,46,54] The median OS at 2 to 4 years ranged between 31% and 50%. Age did not impact rates of NRM, relapse rate, or rates of graft-versus-host disease. For these reasons, chronologic age alone should not be the sole criterion used to determine eligibility for allo-HCT, thought it may impact the choice of conditioning regimen.

Geriatric Assessment

Cancer is a disease associated with aging,[4] and as the older population increases in the United States, more older adults will become candidates for HCT. A need exists to develop evidence-based tools to guide decisions regarding which older adults will be able to tolerate the rigorous course of HCT, and hence potentially enjoy its long-term benefit without succumbing to toxicities.

Standard pre-HCT evaluations provide a detailed assessment of many health-related factors that predict clinical outcomes. However, older patients are predisposed to a unique set of medical and social issues that may not be prevalent in younger patients but could impact outcomes. Cognitive impairment, hearing impairment, falls, and urinary incontinence are rare in younger transplant patients, but much more common in older adults. CGA may help to fill this knowledge gap. Table 2 reviews the components of CGA. CGA can identify older patients with cancer who are at increased risk for morbidity, mortality, and chemotherapy toxicity.[55,56] A pilot study of CGA in older adults undergoing allo-HCT showed that this assessment identifies areas of vulnerability that are not apparent in a routine history and physical examination. Among 166 patients older than 50 years (16%, age >65 years) who were undergoing allo-HCT, 40% reported the need for assistance with instrumental activities of daily living (activities required to maintain independence within the com-

Table 2 Components of a Comprehensive Geriatric Assessment[a]

Functional status
- Activities of daily living
  - ▸ EatingDressing
  - ▸ Continence
  - ▸ Grooming
  - ▸ Transferring
  - ▸ Using the bathroom
- Instrumental activities of daily living
  - ▸ Using transportation
  - ▸ Managing money
  - ▸ Taking medications
  - ▸ Shopping
  - ▸ Preparing meals
  - ▸ Doing laundry
  - ▸ Doing housework
  - ▸ Using the telephone
- Performance status
- Falls
- Gait speed

Psychological state
- Anxiety
- Depression
- Distress

Comorbidities
- Number
- Type
- Severity
- Risk of exacerbation with cancer treatment

Cognitive function
- Capacity for decision-making
- Dementia
- Depression
- Delirium

Medication review
- Polypharmacy
- Potentially inappropriate medications
- Drug interactions

Nutritional status
- Unintentional weight loss
- Low body mass index
- Access to food

Social support
- Emotional support
- Tangible support (assistance with daily tasks)
- Financial support

[a]See NCCN Clinical Practice Guidelines in Oncology for Senior Adult Oncology for additional information (in this issue; to view subsequent updates to these guidelines, visit NCCN.org).

munity); 51% were "pre-frail" and 25% were "frail" based on Fried frailty criteria[57]; and 60% reported weight loss greater than 10%. The authors concluded that performing a CGA before HCT was feasible, with 73% of eligible transplant recipients completing the CGA.[58]

Other studies have evaluated the impact of comorbidity, a specific focus of the CGA, on NRM and toxicity. The HCT-CI, validated among patients receiving allo-HCT, captures pretransplant comorbidities and identifies patients at increased risk for NRM.[49] Comorbidity measures are also predictive in patients undergoing auto-HCT. Among patients with multiple myeloma undergoing auto-HCT, the CCI and the HCT-CI identified patients at increased risk for toxicity and longer length of stay.[59] Further studies are needed to evaluate the combination of CGA factors that can more precisely identify patients at increased risk for toxicity and NRM, and to determine whether specific interventions can decrease this risk. Study of serial CGA throughout treatment may also help predict the short- and long-term impact of transplantation on an older adult's functional status and quality of survival. This information could provide valuable assistance in clarifying the risks and benefits of transplantation for older patients.

Conclusions

The aging of the US population and the increased incidence of hematologic malignancies with age herald an increase in the number of older adults considered for auto-HCT and allo-HCT. With the heterogeneity of aging, chronologic age alone does not consistently predict the toxicity and effectiveness of HCT. Further study will illuminate the utility of CGA in addition to standard pre-HCT evaluations for identifying older adults who are vulnerable to the toxicity of HCT, and may guide interventions to improve the care of older adults with hematologic malignancies.

References

1. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265–276.
2. Kyle RA, Therneau TM, Rajkumar SV, et al. Incidence of multiple myeloma in Olmsted County, Minnesota: trend over 6 decades. Cancer 2004;101:2667–2674.
3. Juliusson G, Antunovic P, Derolf Å, 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.
4. 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.
5. Piccirillo JF, Vlahiotis A, Barrett LB, et al. The changing prevalence of comorbidity across the age spectrum. Crit Rev Oncol Hematol 2008;67:124–132.
6. McCarthy PL, Hahn T, Hassebroek A, et al. Trends in use of and survival after autologous hematopoietic cell transplantation in North America, 1995-2005: significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age. Biol Blood Marrow Transplant 2013;19:1116–1123.
7. Hahn T, McCarthy PL, Hassebroek A, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. J Clin Oncol 2013;31:2437–2449.
8. Waterstrat A, Van Zant G. Effects of aging on hematopoietic stem and progenitor cells. Curr Opin Immunol 2009;21:408–413.
9. Tempescul A, Ianotto JC, Hardy E, et al. Peripheral blood stem cell collection in elderly patients. Ann Hematol 2010;89:317–321.
10. Morris CL, Siegel E, Barlogie B, et al. Mobilization of CD34+ cells in elderly patients (≥ 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. Br J Haematol 2003;120:413–423.
11. Jantunen E. Autologous stem cell transplantation beyond 60 years of age. Bone Marrow Transplant 2006;38:715–720.
12. Magagnoli M, Castagna L, Balzarotti M, et al. Feasibility and toxicity of high-dose therapy (HDT) supported by peripheral blood stem cells in elderly patients with multiple myeloma and non-Hodgkin's lymphoma: survey from a single institution. Am J Hematol 2003;73:267–272.
13. Micallef IN, Stiff PJ, Stadtmauer EA, et al. Safety and efficacy of upfront plerixafor + G-CSF versus placebo + G-CSF for mobilization of CD34(+) hematopoietic progenitor cells in patients ≥60 and. Am J Hematol 2013;88:1017–1023.
14. Kumar SK, Dingli D, Lacy MQ, et al. Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: results from a matched pair analysis. Am J Hematol 2008;83:614–617.
15. 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.
16. Jantunen E, Kuittinen T, Penttilä K, et al. High-dose melphalan (200 mg/m2) supported by autologous stem cell transplantation is safe and effective in elderly (>or=65 years) myeloma patients: comparison with younger patients treated on the same protocol. Bone Marrow Transplant 2006;37:917–922.
17. Mileshkin LR, Seymour JF, Wolf MM, et al. Cardiovascular toxicity is increased, but manageable, during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for patients aged 60 years and older. Leuk Lymphoma 2005;46:1575–1579.
18. 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.

19. Wildes TM, Augustin KM, Sempek D, et al. Comorbidities, not age, impact outcomes in autologous stem cell transplant for relapsed non-Hodgkin lymphoma. Biol Blood Marrow Transplant 2008;14:840–846.
20. Jantunen E, Itälä M, Juvonen E, et al. Autologous stem cell transplantation in elderly (>60 years) patients with non-Hodgkin's lymphoma: a nation-wide analysis. Bone Marrow Transplant 2006;37:367–372.
21. Puig N, Pintilie M, Seshadri T, et al. High-dose chemotherapy and auto-SCT in elderly patients with Hodgkin's lymphoma. Bone Marrow Transplant 2011;46:1339–1344.
22. Sweetenham JW, Pearce R, Phillip T, et al. High-dose therapy and autologous bone marrow transplantation for intermediate and high grade non-Hodgkin's lymphoma in patients aged 55 years and over: results from the European Group for Bone Marrow Transplantation. The EBMT Lymphoma Working Party. Bone Marrow Transplant 1994;14:981–987.
23. Miller CB, Piantadosi S, Vogelsang GB, et al. Impact of age on outcome of patients with cancer undergoing autologous bone marrow transplant. J Clin Oncol 1996;14:1327–1332.
24. Kusnierz-Glaz CR, Schlegel PG, Wong RM, et al. Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies. J Clin Oncol 1997;15:18–25.
25. Buadi FK, Micallef IN, Ansell SM, et al. Autologous hematopoietic stem cell transplantation for older patients with relapsed non-Hodgkin's lymphoma. Bone Marrow Transplant 2006;37:1017–1022.
26. Hosing C, Saliba RM, Okoroji GJ, et al. High-dose chemotherapy and autologous hematopoietic progenitor cell transplantation for non-Hodgkin's lymphoma in patients >65 years of age. Ann Oncol 2008;19:1166–1171.
27. Jantunen E, Canals C, Rambaldi A, et al. Autologous stem cell transplantation in elderly patients (> or =60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry. Haematologica 2008;93:1837–1842.
28. Lazarus HM, Carreras J, Boudreau C, et al. Influence of age and histology on outcome in adult non-Hodgkin lymphoma patients undergoing autologous hematopoietic cell transplantation (HCT): a report from the Center For International Blood & Marrow Transplant Research (CIBMTR). Biol Blood Marrow Transplant 2008;14:1323–1333.
29. Jantunen E, Canals C, Attal M, et al. Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2012;23:166–171.
30. Elstrom RL, Martin P, Rua SH, et al. Autologous stem cell transplant is feasible in very elderly patients with lymphoma and limited comorbidity. Am J Hematol 2012;87:433–435.
31. Andorsky DJ, Cohen M, Naeim A, Pinter-Brown L. Outcomes of auto-SCT for lymphoma in subjects aged 70 years and over. Bone Marrow Transplant 2011;46:1219–1225.
32. 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.
33. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335:91–97.
34. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875–1883.
35. Reece DE, Bredeson C, Pérez WS, et al. Autologous stem cell transplantation in multiple myeloma patients /=60 years of age. Bone Marrow Transplant 2003;32:1135–1143.
36. Lenhoff S, Hjorth M, Westin J, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. Br J Haematol 2006;133:389–396.
37. Offidani M, Leoni P, Corvatta L, et al. ThaDD plus high dose therapy and autologous stem cell transplantation does not appear superior to ThaDD plus maintenance in elderly patients with de novo multiple myeloma. Eur J Haematol 2010;84:474–483.
38. 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.
39. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Blood 2007;109:1395–1400.
40. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. J Clin Oncol 2010;28:2859–2867.
41. Davies SM, Kollman C, Anasetti C, et al. Engraftment and survival after unrelated-donor bone marrow transplantation: a report from the national marrow donor program. Blood 2000;96:4096–4102.
42. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood 2013;121:2567–2573.
43. Wallen H, Gooley TA, Deeg HJ, et al. Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. J Clin Oncol 2005;23:3439–3446.
44. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol 2010;28:405–411.
45. Armand P, Kim HT, Zhang MJ, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. Biol Blood Marrow Transplant 2012;18:280–288.
46. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. JAMA 2011;306:1874–1883.
47. Koreth J, Aldridge J, Kim HT, et al. Reduced-intensity conditioning hematopoietic stem cell transplantation in patients over 60 years: hematologic malignancy outcomes are not impaired in advanced age. Biol Blood Marrow Transplant 2010;16:792–800.
48. Brunner AM, Kim HT, Coughlin E, et al. Outcomes in patients age 70 or older undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Blood Marrow Transplant 2013;19:1374–1380.

49. Sorror ML. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912–2919.

50. Kataoka K, Nannya Y, Ueda K, et al. Differential prognostic impact of pretransplant comorbidity on transplant outcomes by disease status and time from transplant: a single Japanese transplant centre study. Bone Marrow Transplant 2010;45:513–520.

51. Takasaki H, Tanaka M, Tachibana T, et al. Prognostic factors in patients aged 50 years or older undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancy. Int J Hematol 2012;95:291–298.

52. Majhail NS, Brunstein CG, McAvoy S, et al. Does the hematopoietic cell transplantation specific comorbidity index predict transplant outcomes? A validation study in a large cohort of umbilical cord blood and matched related donor transplants. Biol Blood Marrow Transplant 2008;14:985–992.

53. Bayraktar UD, Shpall EJ, Liu P, et al. Hematopoietic cell transplantation-specific comorbidity index predicts inpatient mortality and survival in patients who received allogeneic transplantation admitted to the intensive care unit. J Clin Oncol 2013;31:4207–4214.

54. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 2010;28:1878–1887.

55. 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.

56. 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.

57. 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.

58. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. Biol Blood Marrow Transplant 2013;19:429–434.

59. Labonté L, Iqbal T, Zaidi MA, et al. Utility of comorbidity assessment in predicting transplantation-related toxicity following autologous hematopoietic stem cell transplantation for multiple myeloma. Biol Blood Marrow Transplant 2008;14:1039–1044.

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/37102;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

PostTest Questions

1. Which of the following are strong predictors of toxicities and outcomes in older patients undergoing HCT?
   a. Chronologic age alone
   b. Comorbidities
   c. Functional status
   d. Both b and c
   e. None of the above
2. True or False: Plerixafor improves the rates of stem cell mobilization in older adults with myeloma and lymphoma.
   a. True
   b. False
3. A CGA evaluates which of the following components of a patient's lifestyle?
   a. Cognitive function
   b. Psychological function
   c. Social support
   d. Nutritional status
   e. All of the above