our evolving understanding of the mechanisms by which these symptoms develop, including inflammation (8,9), autoimmune phenomena (10), hormonal influences (11), and neurotoxic effects of specific agents (12,13). However, although research into mechanisms of cognitive dysfunction related to cancer therapy is clearly important and needed, a full understanding of the biology of cancer-related symptoms is not necessary for effective interventions to be employed.

First, identification and treatment of underlying medical and psychological conditions, including endocrine dysfunction, anemia, sleep disturbance, diabetes, and depression, is necessary but sometimes overlooked in the battle against cancer. Second, there are a number of behavioral strategies that are often helpful, including relaxation training to focus attention and reduce stress, exercise, cognitive rehabilitation, and compensatory strategies such as using personal electronic mobile devices or daily planners. Lifestyle changes, including alterations of the work environment, reasonable accommodations in the scholastic environment, and vocational retraining are often very effective. However, mental exercises that are designed and marketed to improve cognitive function, which perhaps provide mental stimulation in general and likely result in improved performance on the specific task, have not been definitively proven to generalize to other aspects of the person's ability to function. Third, pharmacologic treatments, particularly psychostimulants, have been shown to be useful for people with attentional problems and fatigue, if not medically contraindicated. Research into other pharmacologic strategies, including agents that attenuate inflammation or reduce oxidative stress, is ongoing. However, it is important that such agents do not undermine the primary antineoplastic therapy and "feed" the tumor.

A large number of cancer survivors suffer from neurocognitive, emotional, and behavioral symptoms that interfere with their academic, vocational, and social pursuits. These impairments, as demonstrated in the Ganz et al. study (1), commonly involve problems with memory, multitasking, speed of cognitive processing, and the need to use more mental effort to perform routine tasks (all of which also contribute to fatigue and depression). However, many cancer survivors can enjoy improved levels of functioning if properly diagnosed and provided with the right support. Symptom assessment coupled with effective and proactive intervention strategies are a critical component throughout and after cancer treatment.

References

1. Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*. 2013;105(11)791–801.
2. Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biologic correlates of cognitive dysfunction associated with cancer therapy. *Oncologist*. 2008;13:1285–1295.
3. Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev*. 2008;18:121–131.
4. Koppelmans V, Breteler MMB, Boogerd W. Seynaeve C, Gundy C, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol*. 2012;30 (10):1080–1086.
5. Ahles TA, Root JC, Ryan EL. Cancer and cancer treatment-associated cognitive change: an update on the state of the science. *J Clin Oncol*. 2012;30 (30):3675–3686.
6. Jim HSL, Phillips KM, Chait S, Faul LA, Popa MA, Lee Y-H, Hussin MG, Jacobsen PB, Small BJ. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012;30(29):3578–3587.
7. Meyers CA, Wefel JS. Cognitive dysfunction: is chemobrain real? In: Cleeland CS, Fisch MJ, Dunn AJ, eds. *Cancer Symptom Science*. New York: Cambridge University Press; 2011.
8. Lee BN, Dantzer R, Langley KE, et al. A cytokine-based neuroimmunological mechanism of cancer-related symptoms. *Neuroimmunomodulation*. 2004;11:279–292.
9. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2005;104(4):788–793.
10. Dropcho EJ. Update on paraneoplastic syndromes. *Curr Opin Neurol*. 2005;18(3):331–336.
11. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard dose adjuvant chemotherapy in women with breast cancer: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004;100(11):2292–2299.
12. Meyers CA, Kudelka AP, Conrad CA, Gelke CK, Grove W, Pazdur R. Neurotoxicity of CI-980, a novel mitotic inhibitor. *Clin Cancer Res*. 1997;3:419–422.
13. Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. *J Neuropsychiat Clin Neurosci*. 2004;16(2):185–191.

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Can We Identify Predictive Biomarkers for Antiangiogenic Therapy of Cancer Using Mathematical Modeling?

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Angiogenesis (the term referring generically to new blood vessel formation) is a hallmark of all solid tumors (1), and vascular endothelial growth factor (VEGF) is the most prevalent and potent angiogenic growth factor in these tumors (2,3). For this reason, there have been

intense efforts to develop therapies that target the VEGF pathway. Currently, there are nine antiangiogenic drugs approved by the US Food and Drug Administration and one pending approval (Table 1) (4). These agents are antibodies that target VEGF itself (bevacizumab and aflibercept) or its receptor VEGFR2 (ramucirumab), or are tyrosine kinase inhibitors that interfere with VEGFR2 signaling as well as other receptor and cellular kinases. Introduction of these new drugs over the last decade has established antiangiogenic therapy as a novel therapeutic modality, but their implementation has raised several important questions. Why do they work in some cancers and not others? Is the mechanism of action similar when targeting the ligand versus the receptors, or when using specific versus multitargeted drugs? Can any of them completely block the VEGF pathway? What mediates the inevitable escape from therapy? Can we find biomarkers to identify patients who will benefit from these agents or pathways that must be targeted when tumors become refractory to a given antiangiogenic agent?

Most cancer cell–targeted drugs target identifiable oncogenic pathways known to drive tumorigenesis and have corresponding biomarkers related to those pathways that help guide treatment. However, the theoretical advantage of antiangiogenic therapy over these cancer cell–targeted treatments is that it can be applied more broadly, irrespective of the genetic makeup of each cancer. Unfortunately, unlike in the development of anticancer targeted agents—where target is often an identifiable oncogenic signal known to drive tumorigenesis—the clinical development of antiangiogenic agents has not been biomarker-based. This, coupled with the fact that the exact mechanism(s) of benefit of anti-VEGF drugs remain unclear, has resulted in a complete lack of biomarker-based selection of patients for antiangiogenic therapy with anti-VEGF drugs (5,6). Clearly, the approach of indiscriminately using antiangiogenic drugs in all patients with an approved indication limits their overall efficacy, as some patients show inherent resistance.

This raises important concerns for the use of antiangiogenic therapy and makes the identification of mechanistic biomarkers of response a priority. Such a biomarker would allow selection of patients who would experience survival benefits in excess of the 2–5 months seen in the overall population with antiangiogenic therapies. This would likely equal or even surpass the benefits of cancer cell–targeted drugs, which are given in selected populations (eg, patients with *cKIT*, *EGFR*, or *BRAF* mutations or *HER2* amplification) (4). Moreover, it would rekindle the interest for developing antiangiogenic therapies for diseases in which current antiangiogenic drugs have failed in unselected populations (eg,

Table 1. Overview of successful phase III trials of antiangiogenic agents*

Drug	Indication	Improvement in RR (%)	Improvement in PFS (months)	Improvement in OS (months)
Bevacizumab	Metastatic colorectal cancer (with chemotherapy)	10	4.4	4.7
		0	1.4	1.4
		7.8	2.8	2.5
		14.1	2.6	2.1
	Metastatic nonsquamous NSCLC (with chemotherapy)	20	1.7	2.0
		10.3–14.0	0.4–0.6	NS
	Metastatic breast cancer (with chemotherapy)	15.7	5.9	NS
		9–18	0.8–1.9	NS
		11.8–13.4	1.2–2.9	NS
		9.9	2.1	NS
	Recurrent GBM (monotherapy)	Currently only phase II data reported		
	Metastatic RCC (with IFN-α)	18	4.8	NS
		12.4	3.3	NS
Sunitinib	Metastatic RCC	35	6.0	4.6
	GIST	6.8	4.5	NS
	PNET	9.3	4.8	?
Sorafenib	Metastatic RCC	8	2.7	NS
	Unresectable HCC	1	NS	2.8
	Unresectable HCC	2	1.4	2.3
Pazopanib	Metastatic RCC	27	5.0	N/A
	Advanced soft tissue sarcoma	6.0	3.0	NS
Vandetanib	Advanced medullary thyroid cancer	43	6.2	N/A
Axitinib	Advanced RCC	10	2.0	N/A
Regorafenib	Chemo-refractory metastatic colorectal cancer	0.6	0.2	1.4
Aflibercept	Chemo-refractory metastatic colorectal cancer	8.7	2.2	1.4
Cabozantinib	Advanced medullary thyroid cancer	25	7.2	NS
Ramucirumab	Metastatic gastric and gastroesophageal junction cancers†	0.8	0.8	1.4

* GBM = glioblastoma; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; IFN-α = interferon alpha; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PNET = pancreatic neuroendocrine tumor; RCC = renal cell carcinoma. Source: Updated from Jain, 2013 (4).

† Not currently FDA approved.

prostate, pancreatic, brain, or breast cancer). Finally, a predictive biomarker would allow exclusion of patients who do not benefit from antiangiogenic therapy and spare them the toxicities and cost of these drugs.

The importance of these issues has stimulated active research in these areas, producing hypothesis-generating results that could potentially impact the treatment outcome. In an article in this issue of the Journal, Finley and Popel (7) use a computational model to address this problem. They model VEGF kinetics in the relevant physiologic compartments to investigate the distribution in the body of two major soluble VEGF isoforms ($VEGF_{121}$ and $VEGF_{165}$). The model predicts changes in VEGF concentrations in each compartment after intravenous injection of a VEGF blocker. One interesting conclusion is that the concentration of free VEGF is higher in the tumor interstitium than the circulating plasma and is predominantly in the form of $VEGF_{121}$. The model also predicts that tumor VEGF levels can either increase or decrease after anti-VEGF treatment depending on the tumor microenvironment. Collectively, these intriguing results suggest that the rate of VEGF secretion by tumor cells is the major determinant of response and could serve as a predictive biomarker for anti-VEGF drugs.

Limited clinical data lend support to this model. VEGF expression level has been the natural candidate as a biomarker for anti-VEGF drugs, but data have been inconsistent (5). Some studies suggest that circulating VEGF may predict response to anti-VEGF therapy in hepatocellular carcinoma and breast cancer (8,9). Other studies, including many randomized phase III trials, found no association between circulating VEGF and response to the anti-VEGF antibody bevacizumab (10–12). Some studies have measured the levels of purely soluble isoforms (eg, $VEGF_{121}$, not bound to tumor matrix), and have found intriguing associations with outcome (13). Others have not detected any statistically significant association for $VEGF_{121}$ (6,14). Finally, the limited available data on the changes in tumor VEGF levels after antiangiogenic therapy suggest a decrease in VEGF expression by cancer cells (15).

Thus, there is still controversy regarding the value of tumor or circulating VEGF as predictive biomarkers in the clinic, and mathematical models such as presented by Finley and Popel (7) could be valuable tools to help sort out this complex issue. These models can be easily adapted to reflect new empirical information to fine-tune the use of VEGF isoforms as predictive biomarkers. For example, additional factors such as host cells (eg, tumor-associated fibroblasts or myeloid cells) that secrete VEGF could be included (16,17). Also, modeling could be performed at higher resolution to investigate how spatiotemporal variations in VEGF levels might be produced by the microenvironment of each compartment or whether endogenous production of VEGF blockers—such as soluble (s) VEGFR1 (also known as sFLT1)—should be considered (18–23). Finally, modeling might determine whether resistance from antiangiogenic therapy is due to the incomplete blockade of VEGF signaling by analyzing ligand-targeted versus receptor-targeted agents: receptor-targeted agents do not directly interact with VEGF ligand, so their biological effects should not be affected by changes in VEGF secretion of specific isoforms.

A potentially critical factor is the existence of endogenous blockers of VEGFs such as sVEGFR1. In 2009, we proposed circulating plasma sVEGFR1 as a potential biomarker that predicts inherent resistance to anti-VEGF therapies in cancer (22). Indeed, we found in five single-arm phase II studies that cancer patients with high levels of circulating sVEGFR1 had a poor outcome after anti-VEGF therapies with antibodies as well as tyrosine kinase inhibitors (18–23). In some of these studies we found that these patients also experienced fewer side effects, further supporting the notion that high sVEGFR1 levels lower biological activity of anti-VEGF agents irrespective of their mode of action (18,21,23). Moreover, specific single-nucleotide polymorphisms in the *FLT1* gene that are associated with higher VEGFR1 expression are also associated with poor outcomes in phase III studies of bevacizumab (24). It is unclear if the predictions from the currently available computational models support the use of sVEGFR1 or ratio of sVEGFR1 to VEGF as a biomarker.

In summary, the mathematical model of Finley and Popel (7) is a step forward in our understanding of the potential roles of different VEGF isoforms in the tumor and in blood circulation. It also raises many exciting questions about potential biomarkers for anti-VEGF therapies, and emphasizes once again the need for prospective clinical studies to specifically address them.

References

1. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. 2011;473(7347):298–307.
2. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol*. 2002;20(21):4368–4380.
3. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003;9(6):669–676.
4. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. *J Clin Oncol*. doi:10.1200/JCO.2012.46.3653.
5. Jain RK, Duda DG, Willett CG, et al. Biomarkers of response and resistance to antiangiogenic therapy. *Nat Rev Clin Oncol*. 2009;6(6):327–338.
6. Lambrechts D, Lenz HJ, de Haas S, et al. Markers of response for the antiangiogenic agent bevacizumab. *J Clin Oncol*. 2013;31(9):1219–1230.
7. Finley SD, Popel AS. Effect of tumor microenvironment on tumor VEGF during anti-VEGF treatment: systems biology predictions. *J Natl Cancer Inst*. 2013;105(11):802–811.
8. Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2010;28(20):3239–3247.
9. Zhu AX, Sahani DV, Duda DG, et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol*. 2009;27(18):3027–3035.
10. Dowlati A, Gray R, Johnson DH, et al. Prospective correlative assessment of biomarkers in E4599 randomized phase II/III trial of carboplatin and paclitaxel ± bevacizumab in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2006;24S:7027.
11. Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol*. 2006;24(2):217–227.
12. Hegde PS, Jubb AM, Chen D, et al. Predictive impact of circulating vascular endothelial growth factor in four phase III trials evaluating bevacizumab. *Clin Cancer Res*. 2013;19(4):929–937.
13. Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol*. 2012;30(17):2119–2127.
14. Jayson GC, de Haas S, Delmar P, et al. Evaluation of plasma VEGFA as a potential predictive pan-tumour biomarker for bevacizumab. *Eur J Cancer*. 2011;47:S96.

15. Xu L, Duda DG, di Tomaso E, et al. Direct evidence that bevacizumab, an anti-VEGF antibody, up-regulates SDF1alpha, CXCR4, CXCL6, and neuropilin 1 in tumors from patients with rectal cancer. *Cancer Res*. 2009;69(20):7905–7910.
16. Fukumura D, Xavier R, Sugiura T, et al. Tumor induction of VEGF promoter activity in stromal cells. *Cell*. 1998;94(6):715–725.
17. Stockmann C, Doedens A, Weidemann A, et al. Deletion of vascular endothelial growth factor in myeloid cells accelerates tumorigenesis. *Nature*. 2008;456(7223):814–818.
18. Duda DG, Willett CG, Ancukiewicz M, et al. Plasma soluble VEGFR-1 is a potential dual biomarker of response and toxicity for bevacizumab with chemoradiation in locally advanced rectal cancer. *Oncologist*. 2010;15(6):577–583.
19. Meyerhardt JA, Ancukiewicz M, Abrams TA, et al. Phase I study of cetuximab, irinotecan, and vandetanib (ZD6474) as therapy for patients with previously treated metastastic colorectal cancer. *PLoS One*. 2012;7(6):e38231.
20. Raut CP, Boucher Y, Duda DG, et al. Effects of sorafenib on intra-tumoral interstitial fluid pressure and circulating biomarkers in patients with refractory sarcomas (NCI protocol 6948). *PLoS One*. 2012;7(2):e26331.
21. Tolaney SM, Duda DG, Boucher Y, et al. A phase II study of preoperative (preop) bevacizumab (bev) followed by dose-dense (dd) doxorubicin (A)/cyclophosphamide (C)/paclitaxel (T) in combination with bev in HER2-negative operable breast cancer (BC). *J Clin Oncol*. 2012;30:(suppl; abstr 1026).
22. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J Clin Oncol*. 2009;27(18):3020–3026.
23. Zhu AX, Ancukiewicz M, Supko JG, et al. Efficacy, safety, pharmacokinetics and biomarkers of cediranib monotherapy in advanced hepatocellular carcinoma: a phase II study. *Clin Cancer Res*. 2013;19:1157–1166.
24. Lambrechts D, Claes B, Delmar P, et al. VEGF pathway genetic variants as biomarkers of treatment outcome with bevacizumab: an analysis of data from the AViTA and AVOREN randomised trials. *Lancet Oncol*. 2012;13:724–733.

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