Multiple Molecular Targets in Oncology and Integrative Care

Our editorial staff at *Integrative Cancer Therapies* recently received terrific news when we heard that the journal had been accepted for inclusion in *Index Medicus*, after only 1 year of publication. Abstracts of new and past articles from the journal will be appearing in Medline/PubMed beginning in the summer of 2003. Inclusion of a new journal in *Index Medicus* after just a year of publication is unusual; usually a longer track record is required for access to this service, which acts as a quality control mechanism for medical journals. Recognition of *Integrative Cancer Therapies* at this early date is a testament to our hard-working staff, to the quality of articles that have been submitted to the journal, and to the importance of the publication of sound science in this burgeoning area, which is of such critical interest to practitioners and cancer patients alike.

At the recent American Society of Clinical Oncology (ASCO) meeting, in Chicago, participants were abuzz with the results of the latest and most innovative thinking in oncology. Most notably, in a post-media embargo session immediately following the formal closing on the last day of the meeting, attendees heard descriptions of a small revolution in the making: the targeting of multiple molecular mechanisms of tumor growth in new treatment protocols that combine monoclonal antibodies, target-specific therapies, and chemotherapy to impact multiple molecular mechanisms of tumor growth simultaneously and perhaps sequentially. I attended this session with Dr Mark Renneker, another integrative cancer physician who is on the editorial board of this journal (we included a rare after-dark surfing session on Lake Michigan as part of our own nonconference agenda). On one hand, we were less than impressed with the session findings, due to the very preliminary nature of most of the research presented. On the other hand, we were keenly aware that we were firsthand witnesses to a paradigm-shifting event in oncology. With molecular target therapies being among the most significant changes in cancer care in the past 4 decades, this new direction in cancer care—which includes experimental and clinical data supporting the multi-interventional approach—was both a medical breakthrough and an indirect confirmation of integrative cancer care. For what is integrative care if not the recognition of synergistic value in the careful coupling of multiple therapies? In spite of our excitement at the data presented in the special session, though, Dr Renneker and I still had somewhat of a sense of puzzlement and irony, since for most of us specializing in integrative oncology, the use of multitargeted approaches was far from new.

What were some of the papers that were given at the ASCO session? Roy Herbst, of the M.D. Anderson Cancer Center, presented data from a Phase I/II trial using bevacizumab and erlotinib in the treatment of non-small-cell lung cancer.[1] Bevacizumab blocks the action of vascular endothelial growth factor (VEGF), a critical molecular signal regulating angiogenesis. Erlotinib, on the other hand, is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that blocks activation of the EGFR and its downstream signaling pathways, thereby inhibiting tumor growth. Erlotinib also figured in a paper by Michael Prados, in which it is combined with the alkylating agent temozolomide.[2] This combination of a cytotoxic agent with an EGFR tyrosine kinase inhibitor is being explored in a Phase I study of glioblastoma multiforme. Finally, Herbert Hurwitz created a stir with a Phase III study showing increases in survival time of just over 4 months in advanced colorectal cancer using bevacizumab in conjunction with irinotecan, 5-FU, and leucovorin.[3]

The concept of multiple molecular targeting of drugs in oncology is certainly exciting. It is also fraught with difficulties, not the least of which is obtaining funding from drug companies to study 2 of these drugs at a time! I would certainly never dispute the value of studies such as these, though, which may provide increases in survival, and more tolerable treatment, for cancer patients in the future. But, realistically, because of the nature of integrative oncology, the use of multiple molecular targets by integrative physicians has been common for years. Let's look at some recent studies of natural agents, all of which would commonly be found in integrative cancer care programs, to see what advanced molecular targets they may address.

Diet Changes. McCarty recently discussed how a low-glycemic index vegan diet supplemented by fish oil, green tea, selenium, and glycine might address multiple antiangiogenic targets including down-regulation of insulin-like growth factor-1 (IGF-1) activity,

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suppression of endothelial expression of the VEGF receptor Flk-1, inhibition of tumor production of VEGF, suppression of endothelial responsiveness to VEGF and fibroblast growth factor, and inhibition of endothelial cell mitosis mediated by glycine-gated chloride channels.[4] A team from Oxford University demonstrated lowering of serum IGF-1 concentration and elevation of IGFBP-1 and IGFBP-2 in vegan women relative to lacto-ovo-vegetarians and meat-eaters.[5]

Exercise. Barnard et al demonstrated reduction of serum insulin and IGF-1, with elevation of IGF binding protein-1 (IGFBP-1) in men following a low-fat diet/exercise or strenuous exercise groups in comparison to controls.[6] Serum from the diet/exercise and exercise only groups inhibited growth of LNCaP cells and caused elevation of apoptosis in relation to control group serum.

Flaxseed. Flaxseed supplementation decreased extracellular levels of VEGF in nude mice with established implanted human breast tumors; it also reduced tumor growth and metastases.[7] Flaxseed also was shown to down-regulate expression of IGF-1 and EFGR in this model.[8]

Selenium and Broccoli. In a mouse model of multiple intestinal neoplasia, selenium-enriched broccoli activated pro-apoptotic genes linked to p-53, NFkappaB, and AP-1.[9]

Genistein. This isoflavone, found in abundance in soy and other edible legumes, appears to be a single-compound multiple-molecular target inhibitor in itself. In an in vitro model of comedo ductal carcinoma in situ that expresses the HER-2/neu oncogene, genistein was found to down-regulate HER-2/neu-mediated signal transduction, increase expression of the cyclin-dependent kinase inhibitor p161NK4, and induce Bcl-2-dependent apoptosis.[10] It appeared to inhibit survival signaling pathways (p42/p44 ERK and AKT/PKB) in human squamous cancer cell lines exposed to radiation therapy.[11]

Anti-inflammatory Supplements and Diet. Inhibition of production of 5-hydroxyeicosatetraenoic acid (5-HETE) production through the lipoxygenase pathway of the arachidonic acid cascade produces massive apoptosis in prostate cancer cells, including both hormone-responsive and nonresponsive lines.[12] Jeanne Wallace, in the first issue of this journal, showed the multiple ways in which diet and supplements could direct the arachidonic acid cascade away from the production of inflammatory and tumor-promoting prostaglandin products, such as 5-HETE, and toward the production of anti-inflammatory prostaglandins.[13]

Although I could go on at some length in this vein, these few references demonstrate the point under consideration—the diversity of molecular targets addressed in the typical integrative oncology program. What is unfortunate for patients in the usual approach to oncology, even in the ASCO presentations cited above, is that only a few targets are addressed, whereas a tumor may indeed have multiple molecular defects that eventually become of more importance as survival mechanisms, through processes of clonal evolution, in response to narrowly focused treatments. Integrative care, with its ability to target multiple molecular defects, appears to hold the promise of longer-term suppression of this adaptive mechanism. It is up to the integrative oncology community, now, to demonstrate to the wider scientific community the rationale and clinical viability of this approach.

In this issue, Murray Ardies reviews the potential contributions of inflammatory pathways to the development of lung cancers arising from scarring of lung tissue, specifically scarring by tuberculosis organisms. Richard Fleming, on the other hand, offers patient data on the effects of soy, another staple of integrative care, on breast tissue, using the BEST (breast enhanced scintigraphy testing) technique that he has discussed in the pages of this journal in the past. He also uses the same technique in the investigation of the effects of hormone replacement therapy on breast tissue. A review by *ICT* staff members covers the potential applications and limitations of the immune-stimulating herbs echinacea, ginseng, and astragalus in cancer patients.

On a more whole-person focused note, 2 studies on the use of alternative and complementary medicine by prostate cancer patients, from investigators in Canada, provide some insights into the motivations of patients in choosing different pathways from those recommended by conventional medicine. A team headed by Joanna Eng looks at demographics of prostate cancer patients who use complementary and alternative medicine techniques, and explores the sources of information these patients used. An interesting qualitative analysis by Margaret White and Marja Verhoef provides in-depth data on a small group of patients about whom little is known in detail—those patients who delay or avoid conventional treatments for prostate cancer.

Our Integrative Tumor Board in this issue begins with a diagnostic dilemma—a patient with an apparent recurrence of breast cancer that may instead represent a second primary. The medical oncology and

radiation oncology aspects of the diagnosis and treatment of this situation are explored by Barry Boyd and Arica Hirsch, respectively. Judy Fulop presents a naturopathic medicine analysis of the case that focuses on some factors that may have led to the recurrence. Lewis Mehl-Madrona discusses the potential Native American traditional medicine approaches to the patient at a spiritual level, in the context of a general investigation into healing of the mind, body, and spirit. Finally, the Osher Center at the University of California at San Francisco, in conjunction with the University's Breast Center, presents an overview of the comprehensive intervention that their staff would offer to a patient in this situation. It is interesting to see how the integrative approach is implemented in the university setting, and we hope to have more contributions from university-based integrative centers in the future.

References

1. Herbst R. Phase I/II trial evaluating blockade of tumor blood supply and tumor cell proliferation with combined bevacizumab and erlotinib HCl as targeted cancer therapy in patients with recurrent non-small-cell lung cancer. Presented at meetings of the American Society of Clinical Oncology, May 31-June 3, 2003; Chicago Ill.
2. Prados M. Glioblastoma multiforme (GBM): phase I data with erlotinib and temozolomide. Presented at meetings of the American Society of Clinical Oncology, May 31-June 3, 2003; Chicago Ill.
3. Hurwitz H. Antiangiogenic strategies in advanced colorectal cancer. Presented at meetings of the American Society of Clinical Oncology, May 31-June 3, 2003; Chicago Ill.
4. McCarty MF. A wholly nutritional 'multifocal angiostatic therapy' for control of disseminated cancer. *Med Hypotheses.* 2003;61(1):1-15.
5. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev.* 2002;11(11):1441-1448.
6. Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate.* 2003;56(3):201-206.
7. Dabrosin C, Chen J, Wang L, Thompson LU. Flaxseed inhibits metastasis and decreases extracellular vascular endothelial growth factor in human breast cancer xenografts. *Cancer Lett.* 2002;185(1):31-37.
8. Chen J, Stavro PM, Thompson LU. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr Cancer.* 2002;43(2):187-192.
9. Zeng H, Davis CD, Finley JW. Effect of selenium-enriched broccoli diet on differential gene expression in min mouse liver(1,2). *J Nutr Biochem.* 2003;14(4):227-231.
10. Katdare M, Osborne M, Telang NT. Soy isoflavone genistein modulates cell cycle progression and induces apoptosis in HER-2/neu oncogene expressing human breast epithelial cells. *Int J Oncol.* 2002;21(4):809-815.
11. Akimoto T, Nonaka T, Ishikawa H, et al. Genistein, a tyrosine kinase inhibitor, enhanced radiosensitivity in human esophageal cancer cell lines in vitro: possible involvement of inhibition of survival signal transduction pathways. *Int J Radiat Oncol Biol Phys.* 2001;50(1):195-201.
12. Ghosh J, Myers CE. Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells. *Proc Natl Acad Sci U S A.* 1998;95(22):13182-13187.
13. Wallace J. Nutritional and botanical modification of the inflammatory cascade—eicosanoids, cyclooxygenases, and lipoxygenases—as an adjunct in cancer therapy. *Int Cancer Ther.* 2002;1(1):7-37.

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