Metastatic Breast Cancer: How Far We’ve Come

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In order to frame this commentary on Higgins and Wolff’s review of current treatment options for metastatic breast cancer, I started with a PubMed search of Dr. Marty Abeloff’s work from more than 3 decades ago. This was partly motivated by my own curiosity about a leader whose early career was largely unknown to me, and partly by the desire to see whether “the more things change, the more they remain the same.”

Charting the Progress

Where have we traveled over the past 30 years since the publication of Dr. Abeloff’s paper in Cancer Treatment Reports entitled “Treatment of metastatic breast cancer with Adriamycin-cyclophosphamide induction followed by combination therapy”? How far have we come since his 1977 publication, “Psychologic aspects of the management of primary and metastatic breast cancer” in Progress in Clinical Biological Research?

In their review, Higgins and Wolff chart the progress in the management of metastatic breast cancer. They begin with comments on the diagnostic evaluation of patients presumed to have metastatic disease, examine the requisite studies used in making a diagnosis and monitoring response to treatment, and cite the lack of high-level evidence for the use of serum tumor markers for both monitoring patients after adjuvant therapy as well as assisting in guiding management of metastatic disease.

Regarding the latter, the writers seem to adhere to the conservative guidelines espoused by expert panels.[1] In the “real world,” there is significant use of serum tumor markers in both these settings (despite the guidelines). I would suggest that the true impact of these biomarkers on both morbidity and mortality is not adequately studied—the case has not been proven, nor has it been disproven. Their widespread use in conjunction with history, physical examination, and radiographic studies seems to reflect the fact that most practitioners involved in the care of patients with breast cancer are both scientists and artists; they use any and all tools that are available to them to benefit patients in the absence of adequate evidence to the contrary.

One Size Does Not Fit All

Higgins and Wolff address the role of endocrine therapy in broad terms. We have learned from numerous prior trials that combinations of cytotoxic chemotherapy and antiestrogen therapy do not seem to significantly improve outcomes as compared to either modality alone. Indeed, current trials are exploring the potential to augment the efficacy of antiestrogen therapy with targeted therapies (against angiogenesis and HER family receptors, among others) driven by strong preclinical biologic rationale and data. Much study on the value of combination vs cytotoxic chemotherapy has transpired since Marty Abeloff first reported on multidrug combinations, and what has emerged is a sense that a debate on the merits of one approach vs the other is somewhat contrived. Indeed, the heterogeneity in the biology and behavior of metastatic breast cancer strongly argues for flexibility in chemotherapy strategies.[2] One size does not seem to fit all.

The authors review our expanding repertoire of chemotherapeutic agents, from the emergence of
the taxanes to the utility of capecitabine (Xeloda) and gemcitabine (Gemzar) and the recent introduction of ixabepilone (Ixempra), the first epothilone in clinical use. It is interesting to this reviewer that Dr. Abeloff authored a review article on vinorelbine in metastatic breast cancer in 1995 (Seminars in Oncology). This is but one example of numerous agents with meaningful activity in metastatic breast cancer that are now commonly used but were never approved by the US Food and Drug Administration.

Higgins and Wolff overview the more recent integration of targeted agents such as trastuzumab (Herceptin), lapatinib (Tykerb), and bevacizumab (Avastin) into the management of metastatic breast cancer. One wonders whether Dr. Abeloff could have envisioned such therapies at the outset of his career. During my own fellowship training in the early 1990s, there was much skepticism regarding the potential for monoclonal antibodies as cancer treatment. Perhaps the lesson here is that persistence pays.

In the pre-HER2 era, “triple-negative” breast cancer was simply hormone receptor–negative breast cancer (“double-negative”?). Higgins and Wolff cite some embryonic clinical studies attempting to focus on this newly designated subset of breast cancer, where antiestrogens and HER2-targeted therapies need not apply. Certainly, there is still significant heterogeneity within the group of cancers we commonly call triple-negative. A greater understanding of these differences will undoubtedly inform the development of rational treatment strategies for such patients. At Memorial Sloan-Kettering Cancer Center, we are exploring the possibility of antiandrogen therapy in some estrogen receptor-negative patients whose breast cancers overexpress the androgen receptor.

‘Treat the Patient’

Reflecting on Marty Abeloff’s busy and productive career, and the thoughtful review by his colleagues at Johns Hopkins, I am impressed with both how far we have come in the management of metastatic breast cancer, and also how far we still have to go. Our inability to cure the vast majority of patients with advanced breast cancer in many ways makes me circle back to his early papers on the psychological aspects of breast cancer care. As complex signal transduction pathways are untangled, and rational (and expensive) combinations of targeted agents are developed in the effort to fight metastatic breast cancer, we should not lose our focus on this very important aspect of breast cancer care—treat the patient, not merely the disease. Judging from the testimonies I have heard from several patients who found their way from Baltimore to New York, as well as from his colleagues, Marty Abeloff did both of these jobs supremely well.

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