The Continuing Challenge of Metastatic Breast Cancer

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Breast cancer is the most common cancer in women living in the developed world. One in eight women will be diagnosed with breast cancer during their lifetime. The majority of newly diagnosed patients have early-stage disease.

Biopsy and Biology

The first point of interest raised by Higgins and Wolfe concerns the role of biopsy in metastatic disease. While this is of particular importance to confirm the diagnosis in the setting of isolated solid organ metastases, it is also useful in furthering our understanding of the molecular biology of metastatic breast cancer and its treatment.

Characteristic patterns of metastatic spread are recognized among the subtypes of breast cancer. For example, estrogen receptor (ER)-positive disease frequently metastasizes to bone only, whereas HER2-positive disease is associated with brain metastases. What is unclear is whether there is a direct correlation between the tumor subtypes seen in primary breast cancer and metastatic disease. Does the biology of the primary determine the behavior of metastatic disease or does metastatic disease represent an evolution or shift in the biology of breast cancer?

Evidence of tumor evolution can be observed in ER-positive primary breast cancers presenting with metastases that no longer express the estrogen receptor.[3-5] Similarly, discordance in HER2 status has been observed between primary tumors and metastatic disease at rates of up to 29%.[6] Biopsy of recurrent disease may be more important in the management of metastases than we think, particularly as newer targeted biologic therapies become available.

Expanded Armamentarium

Overall, 5-year survival for breast cancer has risen by 2.2% annually since 1990.[1] However, improvements in outcome for patients with metastatic disease are more difficult to accurately quantify. A positive trend in 5-year survival for patients with stage IV disease has been observed, suggesting that systemic therapy is making an impact.[1]

The review by Higgins and Wolfe details the range of agents currently available for the treatment of metastatic disease. The arsenal has expanded from a mere two drugs in the 1950s—cyclophosphamide and methotrexate—to the more than 20 active agents now available. The most recent additions include the cytotoxics ixabepilone (Ixempra) and nab-paclitaxel (Abraxane) and the new family of biologic agents, including trastuzumab (Herceptin), bevacizumab (Avastin), and lapatinib (Tykerb). Decision-making is simple when there is only one therapeutic modality available (as radiation therapists will attest!), but with increasing options comes increasing complexity.

Targeted Therapy

Since the time of Beatson, breast cancer has led the field among solid tumors in terms of incorporating targeted/individualized therapy into everyday clinical practice. The authors have
identified the growing number of biologic therapies available, including those targeting ErbB2, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF).

The role of trastuzumab for the treatment of HER2-positive disease has been established and is clearly delineated by Drs. Higgins and Wolff. However, the authors state that the sequencing of trastuzumab and chemotherapy as first-line treatment for metastatic disease is yet to be tested. While this is formally correct, the seminal paper published by Slamon et al evaluating trastuzumab in first-line therapy for metastatic disease provides some evidence in support of concurrent therapy. In this study, patients with newly diagnosed metastatic disease were randomized to receive chemotherapy alone or chemotherapy plus trastuzumab. Patients were permitted to cross over from the chemotherapy-alone arm following progression of disease to receive salvage trastuzumab, and most did. Despite this, patients who received chemotherapy plus trastuzumab upfront had a longer median survival (25.1 vs 20.3 months, P = .046) and a 20% reduction in the risk of death.[7] This indirectly supports the use of concurrent treatment.

The roles of bevacizumab, anti-EGFR therapy, and multitargeted tyrosine kinase inhibitors (TKIs) are considerably less certain. The sequencing/combination of these drugs with conventional cytotoxics will form the basis of future clinical trials, and much remains to be learned.

Treatment Sequence and Duration

Increasing complexity in the treatment of metastatic breast cancer extends beyond choice of agent to include sequencing and duration of therapy, about which many questions remain to be answered. For example, on initiation of systemic chemotherapy it is standard practice to discontinue antiestrogens. An alternative approach is standard in the management of hormone-refractory prostate cancer, where luteinizing hormone-releasing hormone (LHRH) analogs are continued, as it is felt that disease progression is caused by the development of a subset of resistant cells from a population of tumor cells responsive to androgen blockade. Could this principle apply to ER-positive breast cancer?

Similar questions have been posed in relation to the duration of trastuzumab therapy for HER2-positive disease. A trial reported by von Minckwitz et al recently evaluated time to progression (TTP) in patients with HER2-positive metastatic breast cancer following progression on trastuzumab. Patients were randomly allocated to capecitabine (Xeloda) or capcitabine plus continued trastuzumab. Preliminary results suggest a trend toward benefit in TTP (24 vs 33 weeks) with continued trastuzumab in combination with chemotherapy.[8] As other biologic therapies emerge, we may have to formally address issues of continuation and reintroduction of treatments during which the disease has already progressed.

Conclusions

Regardless of our successes in treating early-stage breast cancer, metastatic disease will continue to present a clinical challenge. Strides have been made in treatment, and patients now have a wide range of therapeutic options available. Although treatment is not yet curative, the best palliation is often achieved by effective systemic therapy. Expanding our understanding of the biology of metastatic disease will allow rational sequential therapy tailored to the individual. Superior survival, relief of symptoms, and improved quality of life will clearly follow.

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