

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Update on the Management of Inflammatory Breast Cancer

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H&O What is the clinical presentation of inflammatory breast cancer?

AB The typical patient with inflammatory breast cancer presents with a very brief history of symptoms. The breast appears visibly inflamed and red, may be slightly tender to the touch, and the patient may notice a change in the size of the breast. Often when these patients are seen by the family physician, the initial diagnosis is mastitis or infection in the breast. When we see these patients, they have often received antibiotic therapy for some time, but the symptoms are worsening. At that point, the index of suspicion is generally high enough for the physician to recommend a biopsy to determine if there is carcinoma rather than infection. The diagnosis is not made by screening mammography. Most of the time, the disease is detected by the patient, who notices that the breast is warm and tender and displays skin changes, which causes the patient to go to the physician.

Inflammatory breast cancer is actually a misnomer because there is no pathophysiologic inflammation. The skin appears red, inflamed, and edematous because the tumor cells are invading the lymphatic channels and small blood vessels in the skin. These tumor emboli cause edema and clogging of the lymphatic channels and small blood vessels, resulting in an appearance similar to that of an infection.

H&O What is the incidence rate of inflammatory breast cancer?

AB The incidence of this disease is very low. Of all breast cancers, only 1–6% are classic inflammatory breast cancer. It is important to differentiate these patients from those

with locally advanced breast cancer. A locally advanced breast cancer that progresses if left untreated may begin to resemble inflammatory breast cancer. However, patients with inflammatory breast cancer typically progress from a normal to a swollen breast in a few weeks' time. A patient with locally advanced breast cancer will notice a mass in the breast for months, or possibly longer, which progressively enlarges, leading to skin involvement. This is stage IIIB disease, which is noninflammatory, and the prognosis for this subset of patients is quite different from that of patients with inflammatory breast cancer.

H&O Can you describe the evolution of treatment for inflammatory breast cancer?

AB The historic literature shows that inflammatory breast cancer was a uniformly fatal disease, which, in spite of local therapy, rapidly developed both local and distant recurrences. Within 2 years, the majority of patients with inflammatory breast cancer would die from disseminated disease. Once we entered the era of systemic therapy, the prognosis for these patients changed dramatically. Today, these patients are treated with a combined-modality approach. Approximately 30–40% of treated patients remain alive and free of disease for a period of 5–15 years. Thus, although the disease was previously fatal, with appropriate diagnosis and therapy it can now be cured in a significant fraction of patients.

H&O Can you describe the combined-modality approach to treating inflammatory breast cancer?

AB At our center, after the biopsy and diagnosis, patients are referred to our Multidisciplinary Breast Planning Clinic, where they are examined by a surgeon, a radiotherapist, and a medical oncologist. The pathology and diagnostic imaging studies are reviewed. Each patient has a complete staging work up, which includes hematology and chemistry profiles, bilateral mammograms, chest x-ray, bone scan, and computed tomography of the abdomen to ensure the absence of overt distant metastases. Patients are treated with preoperative systemic chemotherapy. Our standard regimen is a three-drug combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) for up to six cycles. In sequential studies over the years, we have found that FAC chemotherapy followed by taxane-

based therapy (paclitaxel) can further improve disease-free survival. In our experience, this combined-modality approach is successful in a sizable fraction of patients. After the delivery of preoperative systemic chemotherapy, most of these patients are technically operable and some may go into complete clinical remission and the breast will appear normal again. In responders, the local therapy usually includes a mastectomy followed by radiation therapy. If the tumor is hormone receptor–positive, we will administer appropriate endocrine therapy for up to 5 years.

Due to the availability of the HER2/neu monoclonal antibody trastuzumab (Herceptin, Genentech), it is important to know not only whether the cancer is hormone receptor–positive or –negative, but also whether it is HER2/neu-positive or –negative. If the cancer is HER2/neu-positive, then we include trastuzumab in the treatment, possibly concomitant with the taxane phase of therapy. After the completion of systemic chemotherapy, we offer local therapy, which includes irradiation after surgery to reduce the risk of local recurrence.

H&O What are the biologic and clinical differences between inflammatory breast cancer and other breast cancers?

AB There are evolving data that suggest that inflammatory breast carcinomas may be biologically different to some degree from the more common breast carcinomas. For example a higher fraction of patients with inflammatory breast cancer have tumors that are hormone receptor–negative; p53, CerbB2, E-cadherin, nuclear factor kappa B–related genes, and RhoC-GT-pase are overexpressed in patients with inflammatory breast cancer. A large proportion of tumors don't express Wisp3. The vascular endothelial growth factor receptor (VEGFR) is overexpressed in a higher fraction of patients with inflammatory breast cancer than in those with more common breast carcinomas. VEGFR has been a research target, and ongoing studies are evaluating VEGFR-targeted agents in this disease. One recently completed trial examined lapatinib (GlaxoSmithKline) in this disease. Nevertheless, we do not yet definitively know the major biological differences between these cancers. We are slowly beginning to understand the biology, and I think that in the near future we may be able to exploit some of the pathways that are uniquely amplified and develop selective therapies for inflammatory breast cancer patients.

H&O What is the role of p53 as a prognostic factor in this cancer?

AB p53 is elevated in a proportion of patients with inflammatory breast cancer and may have some prognos-

tic value. However, in general, prognostic factors have not been examined prospectively in any study. Most of the studies of inflammatory breast cancer are small series, in which researchers have tried to make sense of the disease. I think in the future we need to look at prognostic factors in a prospective manner.

H&O How does the rarity of inflammatory breast cancer affect research into its treatment?

AB In 30 years we have treated close to 200 patients with this disease at M. D. Anderson Cancer Center and examined the outcomes in small sequential studies. As an example of our own retrospective examination of data, we looked at the characteristics of patients who achieved long-term remissions. We did fine-needle aspirations to find out if there were tumor cells in the lymph nodes or not. If the tumor cells had been present at the beginning of treatment but then not present after systemic therapy (ie, if the lymph nodes became sterile and showed no evidence of residual disease), the patients did extremely well. Over 80% of such patients were alive and free of disease 5–10 or more years after therapy. This represents a dramatic change from the earlier rates, in which 100% of patients died within 2 years. To conduct an effective prospective trial, we as researchers need to pool our efforts and construct multi-institutional or multinational studies, which may be able to answer some questions about the disease in a shorter period of time.

H&O Where do you see the diagnosis and treatment of inflammatory breast cancer headed in the future?

AB I think in the future we need to study these tumors more carefully and systematically to define specific biologic aspects that are unique to this cancer compared to noninflammatory breast cancer and exploit those pathways and develop specific therapies. We're not there yet, but such advances may not be far away because this carcinoma is assessable by biopsy.

Suggested Readings

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