Review article
UDC: 618.19-006:615-085:616-037

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Inflammatory breast cancer - where are we now?

KEYWORDS: Breast Neoplasms; Combined Modality Therapy; Treatment Outcome; Antineoplastic Agents

ABSTRACT

Inflammatory breast cancer is perhaps the most aggressive form of breast neoplasm, with a poor prognosis. Clinically, inflammatory breast cancer is characterized by erythema and edema of the skin of the breast, called "peau d`orange", with or without an associated palpable mass. This form represents 1% to 6% (doubled during the past two decades) of all newly diagnosed breast malignancies and is often considered together with local advanced breast cancer, despite specific differential features. The reported 5-year survival rates range from 10% to 75%. On mammography, a diffuse increase in density and skin thickening may be present. Pathologic confirmation of invasion of dermal lymphatics by malignant cells can help distinguish this condition from benign mastitis. Most inflammatory breast cancers are on biopsy poorly differentiated ductal carcinomas, mainly estrogen and progesterone receptor negative. HER2/neu-overexpression and p53 gene mutations are frequently present. The probability of axillary node involvement is approximately 90%. Contralateral breast cancer develops in 25% to 50% of the patients, usually in the presence of metastases. Inflammatory breast cancer has a high rate of locoregional recurrence after surgery and/or radiotherapy and the rapid appearance of distant metastases. However, long-term survival is possible for these patients if treated with multimodality therapy including polychemotherapy, mastectomy, and loco-regional radiotherapy. The optimal sequencing of combined modality therapy has not been determined. Although not all patients are candidates for such a regimen (often due to progression during treatment), for those that complete all phases of therapy, more than one-third will be alive without disease at 10 years.

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The manuscript was received: 28. 08. 2003.

Accepted for publication: 10.09.2003.

INTRODUCTION

Inflammatory breast cancer is perhaps the most aggressive form of breast neoplasm, with a poor prognosis reported historically. Lee and Tannenbaum (1), in their paper printed in 1924, used the term "inflammatory breast cancer" for describing the clinical entity.

CLINICAL PRESENTATION

Clinically, inflammatory breast cancer is characterized by erythema and edema of the skin of the breast, called "peau d`orange", with or without an associated palpable mass (2). Infiltration of the dermal lymphatics is often seen, but its documentation is not necessary for a diagnosis of inflammatory carcinoma (3). Inflammatory breast cancer is characterized by a rapid onset often associated with palpable axillary adenopathy and distant metastases (4). This form represents 1% to 6% of all newly diagnosed breast malignancies and is often considered together with local advanced breast cancer, despite specific differential features (5,6). The Surveillance, Epidemiology and End Results program recently reported data estimates that the incidence of inflammatory breast cancer has approximately doubled during the past two decades (7). The reported 5-year survival rates range from 10% (8) to 75% (9).
The absence of well-defined tumor often suggests an "inflammatory" etiology. These patients often are treated with antibiotics for several weeks before the appropriate diagnosis is made, because of the extensive inflammatory signs without the signs of malignant neoplasm. Most inflammatory breast cancers present as diffuse infiltration of the breast without well-defined tumor (staged as IIIB breast cancer).
On mammography, a diffuse increase in density and skin thickening may be present. Pathologic confirmation of invasion of dermal lymphatics by malignant cells can help distinguish this condition from benign mastitis. Most inflammatory breast cancers are on biopsy poorly differentiated ductal carcinomas and are estrogen and progesterone receptor negative. HER2/neu-overexpression and p53 gene mutations are frequently present. Compared with non-inflammatory local advanced breast cancer, the median thymidine -labeling index is significantly higher for inflammatory breast cancer. A history of rapid onset (less than a couple of months) often is used to differentiate inflammatory breast cancer from local advanced breast cancer with secondary inflammatory features. This differentiation is important since some of the secondary inflammatory breast cancers follow an indolent course and often are hormone sensitive.
The probability of axillary node involvement is approximately 90%. Contralateral breast cancer develops in 25% to 50% of the patients, usually in the presence of metastatic disease.

TREATMENT

Inflammatory breast cancer is characterized by a high rate of locoregional recurrence if treated with surgery and/or radiotherapy and the rapid appearance of distant metastases. The local recurrence rate had been 50% to 80%, metastases had developed in more than 90% of the cases in less than 2 years, and 5-year survival rates had been consistently less than 5% (10) before systemic therapy was introduced in the combined-modality treatment protocols. With the development of induction chemotherapy-containing strategies, a dramatic change occurred in the natural history of inflammatory breast cancer. The results for patients treated with combined modality therapy are summarized by Perez et al. (11) as a retrospective analysis of 179 patients treated with a variety of approaches, including 86 patients treated with chemotherapy, surgery and irradiation. For these patients, the 10-year disease-free survival rate was 35%. A 10-year survival and disease-free survival rate of 32% and 19%, respectively, among 223 inflammatory breast cancer patients treated with chemo- and radiotherapy were reported by the Institut Curie (12). Twenty-year results were reported from the M.D. Anderson Cancer Center for

patients treated under a series of 4 protocols including chemotherapy and local therapies (13). The disease-free survival rate at 15 years was 28%. They did not note any impact on survival with the use of surgery in addition to radiotherapy. The study of a 10-year outcome after combined-modality treatment for inflammatory breast cancer by Harris EE et al. (14) documented a 10-year overall survival rate of 35% and a 10-year relapse free survival rate of 34%.

PROGNOSIS

The response to chemotherapy is an important predictor of outcome. Data from some studies suggest that responses were more common in patients with aneuploid tumors and in those with high proliferative fraction. Response to induction chemotherapy was found by all studies to predict longer disease-free and overall survival. In a study from M.D. Anderson of 63 patients treated with doxorubicin-based chemotherapy and radiotherapy, including 21 patients also undergoing mastectomy, the response to chemotherapy was the most important predictor of relapse-free and overall survival (15). Those patients with either a complete or partial clinical remission after chemotherapy had a median survival of 31 months, compared with 19 months for those with less than a partial response. A separate study by this group in 61 patients, 46 of whom specifically completed planned treatment with induction chemotherapy, mastectomy and postoperative irradiation, reported a 16% complete clinical or pathologic response rate and a 39% no-response rate (16). After long-term follow-up, this group further reported a 15-year disease-free survival rate of 44% in complete responders to any induction chemotherapy, with 31% in partial responders and 0% for those with no response (13). In the study of Eleanor et al. (14), authors analyzed the outcomes by pathologic complete response, defined as no pathologic evidence of cancer in either the breast or lymph nodes at the time of mastectomy. This study did not include any nonresponders to neoadjuvant chemotherapy, although 2 patients included in the analysis had progression outside the involved breast after chemotherapy during preoperative irradiation. Both methotrexate-based and doxorubicin-based induction regimens were used, depending mainly on the year of treatment. No difference was noted in the response rates based on the type of chemotherapy regimen used for induction; 15 (28%) patients had a pathologic complete response, including 2 who had clinical signs of disease at the completion of induction chemotherapy whose complete response was achieved after preoperative irradiation. The 10-year survival of patients with a pathologic complete response was superior to those who had any residual disease in the breast or lymph nodes (46% vs. 31%, $p=0.09$).

Most combined-modality treatment schedules for inflammatory breast cancer consist of induction chemotherapy followed by irradiation of the breast and regional lymphatics and additional adjuvant chemotherapy. Others include a total mastectomy after 3 or 4 cycles of chemotherapy. By definition, protocols that do not include a mastectomy offer breast-conserving therapy. However, this is done at the expense of higher doses of radiotherapy and its expected late toxicity, as well as suboptimal cosmetic result. Because skin edema, erythema, and ridging persist in most patients and because inflammatory tumors often are diffuse and poorly defined, lumpectomy or quadrantectomy are not practical options. In addition, limited data suggest that local failure rate may be higher after breast conserving therapy. Therefore, the standard and preferred surgical modality is mastectomy.

DISEASE OUTCOME

Multimodality therapy delivered with curative intent is the standard of care for patients with inflammatory breast cancer. Initial surgery is generally limited to biopsy to permit the determination of histology, ER/PR levels and HER-2/neu overexpression. Initial treatment with anthracycline-based chemotherapy and/or taxane-based therapy is the standard (13). For patients who respond to induction chemotherapy, local therapy may consist of total mastectomy with axillary lymph node dissection, followed by postoperative radiation therapy to the chest wall and regional lymph nodes. Subsequent systemic therapy may consist of further chemotherapy. Hormone therapy should be administered to patients with hormone sensitive tumors.

In conclusion, the optimal sequencing of combined modality therapy has not been determined. Although not all patients are candidates for such a regimen (often due to progression during treatment), for those that complete all phases of therapy, more than one-third will be alive without disease at 10 years.

Acknowledgement:

I would like to thank Dragan Trajković, BA, research assistant, for his technical help and English proofreading of this paper.

REFERENCES

1. Lee B, Tannenbaum N. Inflammatory carcinoma of the breast: A report of twenty-eight cases from the breast clinic of Memorial Hospital. Surg Gynecol Obstet 1924;39:580-95.

2. Fleming ID, Cooper JS, Henson DE et al, editors. Breast. In: AJCC staging manual. Philadelphia: Lippincott-Raven; 1997. p. 173.

3. Bonnier P, Charpin C, Lejeune C. Inflammatory carcinomas of the breast: A clinical, pathological or a clinical and pathological definition? Int J Cancer 1995;62:382-5.

4. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer. A review. J Clin Oncol 1992;10:1014-24.

5. Lopez MJ, Porter KA. Inflammatory breast cancer. Surg Clin North Am 1996;76:411-29.

6. Levine PH, Steinhorn SC, Ries LG, Aron JL. Inflammatory breast cancer: The experience of the Surveillance, Epidemiology and End Results (SEER) program. J Natl Cancer Inst 1985;74:291-7.

7. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer institute, 1975-1992. Cancer 1998;82:2366-72.

8. Fields JN, Perez CA, Kuske RR, Fineberg BB, Bartlett N. Inflammatory carcinoma of the breast: Treatment results on 107 patients. Int J Radiat Oncol Biol Phys 1989;17:249-55.

9. Zylberberg B, Salat-Baroux J, Ravina JH, Dormont D, Amiel JP, Diebold P et al. Initial chemoimmunotherapy in inflammatory carcinoma of the breast. Cancer 1982;49:1537-43.

10. Singletary SE, Ames FC, Buzdar AU. Management of inflammatory breast cancer. World J Surg 1994;18:87.

11. Fisher B, Ravdin RD, Ausman RK et al. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. Ann Surg 1968;168:337.

12. Palangie T, Mosseri V, Mihura J, Campana F, Beuzeboc P, Dorval T et al. Prognostic factors in inflammatory breast cancer and therapeutic implications. Eur J Cancer 1994;30:921-7.

13. Ueno NT, Buzdar AU, Singletary SE, Ames FC, McNeese MD, Holmes FA et al. Combined-modality treatment of inflammatory breast cancer. Twenty years of experience at M.D. Anderson Cancer Center. Chemother Pharm 1997;40:321-9.

14. Harris EE, Schultz D, Bertsch H, Fox K, Glick J, Solin LJ. Ten-year outcome after combined modality therapy for inflammatory breast cancer. Int J Radiat Oncol Biol Phys 2003;55(5):1200-8.

15. Fastenberg NA, Martin RG, Buzdar AU, Hortobagyi GN, Montague ED, Blumenschein GR et al. Management of inflammatory breast cancer: A combined-modality approach. Am J Clin Oncol 1985;8:134-41.

16. Thoms WW Jr, McNeese MD, Fletcher GH, Buzdar AU, Singletary SE, Oswald MJ. Multimodal treatment for inflammatory breast cancer. Int J Radiat Oncol Biol Phys 1989;19:739-45.