Ulcerative locally advanced breast cancer: the efficacy of combined anthracycline-based and hormonal therapy

D. Kakagia[1], *Ph.D.*; **M. Trichas**[2], *Ph.D.*; **N. Papadopoulos**[3], *Ph.D.*; **A Tsalkidis**[3], *Ph.D.*; **T. Jivannakis**[4], *M.D.*; **D. Tamiolakis**[3], *Ph.D.*

[1]*Department of Surgery* [2]*Department of Oncology* [3]*Thraki Medical Center*
Department of Histology- Embryology, Democritus University of Thrace, Alexandroupolis
[4]*Department of Pathology, Drama Hospital (Greece)*

Summary

Aim: In the literature there are numerous large prospective studies on patients with locally advanced breast cancer, however little is reported on the management of ulcerative breast cancer. The aim of this study was to evaluate the employment of combined anthracycline-based chemotherapy and hormonal therapy in ulcerative locally advanced mammary carcinoma.

Patients and methods: Four patients, aged from 67 to 83 years, presented with ulcerative breast cancer resulting in breast destruction. Histological examination of biopsy specimens revealed highly differentiated estrogen receptor-positive ductal carcinomas. All tumours were classified as locally advanced since there was no clinical or radiologic evidence of distant metastasis in any of the patients.

Due to their religious beliefs all patients refused any other treatment but chemotherapy.

In these patients hemostasis and reduction of bacterial overgrowth were followed by administration of anthracycline-based chemotherapy and hormonal therapy.

Results: All patients responded well; ulcer healing and partial remission were achieved for a period ranging from 19 to 28 months before disease progression.

Conclusion: There is clinical evidence from this study that the combination of anthracycline-based palliative chemotherapy coupled with tamoxifen is beneficial for patients with inoperable ulcerative breast cancer.

Key words: Locally advanced breast cancer; Anthracyclines; Ulcerative breast cancer; Silver-charcoal dressings.

Introduction

Despite widely applied screening programs in European countries aiming at early detection of breast cancer, there is still a high percentage of almost 20% of patients who first present with metastatic or locally advanced disease [1, 2]. Ulcerative breast cancer is observed in approximately 50% of male and 6-15% of female patients at first consultation [2, 3]. However, almost 50% of women over 70 first present with advanced breast disease [4]. Quite often patients with ulcerative breast cancer are first referred to a specialist due to bleeding from the exulcerated breast. Bacterial infection of breast ulcerations mainly by anaerobes is the rule and renders these lesions malodorous and difficult to heal [5-7].

The last few years there has been increasing evidence in the literature that chemotherapy with or without hormonal therapy is effective in locally advanced breast cancer (LABC), either as first line or as palliative therapy [1, 5, 8-10]. Herein four patients with ulcerative LABC in whom palliative chemotherapy and hormonal therapy resulted in partial remission of the disease and better quality of life are presented.

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Patients and Methods

Between August 2001 and March 2004 four female patients, 67-83 years of age, presented at the Breast Clinic of Thraki Medical Centre with exulcerated breast tumours (Figure 1). All patients, three refugees and one financial immigrant, were members of a religious cast and due to their beliefs had never had breast examination by a specialist before, though they had first noticed breast lumps at self-examination from two to four years prior to admission.

In all patients the involved breast was firm and fixed to the overlying ulcerated skin but not to the anterior chest wall. Lesions were necrotic and malodorous. In three patients there were several palpable lumps in the controlateral breasts. All of them had numerous palpable axillary lymph nodes bilaterally.

Control of bleeding was achieved by CO_2 laser and biopsies were obtained. Microbiological cultures of swabs obtained by the ulcerated discharging surfaces revealed mixed bacterial flora with prevalence of pseudomonas. Histology of biopsy specimens documented well-differentiated ductal breast carcinomas, estrogen receptor positive. Tumours were classified as locally advanced, since clinical and radiologic staging was surprisingly unevident of any visceral or bone metastases.

Patients were reviewed by the multidisciplinary oncologic committee and therapeutic options were discussed with them. As all patients refused any other treatment, haemostasis and local ulceration management were followed by anthracycline-based chemotherapy and hormonal therapy. Metronidazole gel was used twice daily on the ulcerated surface during the first three days in order to control growth of anaerobes in combination with hydrocolloid dressing to control exudates. On the

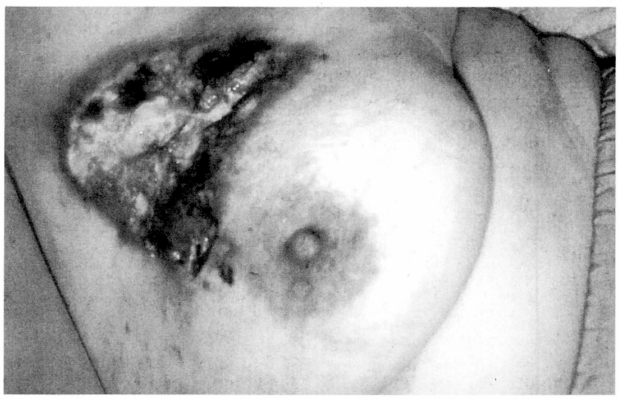

Figure 1. — Exulcerated breast with completely destructed upper lateral quadrant. Necrotic eschars are ideally removed by autolytic debridement using silver-charcoal dressings.

fourth day and thereon silver–charcoal semipermeable dressings (Contreet-H by Coloplast) were applied on the breast in order to enhance autolytic debridement and control bioburden.

Within the first week all patients were started on a CEF chemotherapy regimen (600 mg/m^2 cyclophosphamide, 60 mg/m^2 epirubicin, 600 mg/m^2 fluorouracil). Six courses of CEF were administered in total, each with a three-week interval, while the patients simultaneously received per os tamoxifen 20 mg/day.

Results

The tumour size was significantly reduced after the fourth chemotherapy session in all patients. At the end of sessions partial ulcer healing was observed in three patients and complete in one. On discharge all patients were able to return to their daily routine activities.

Patients were followed up every three months and for 19-28 months the disease was in remission, enabling self-care and full participation in social life. In one patient elevated CA 15-3 and CA-125 values were found without any clinical evidence of local recurrence, whereas in the other three patients elevated marker values were associated with local recurrence. All four patients refused any further treatment. One patient died of advanced disease having missed two follow-up appointments.

Discussion

Malignant breast destruction is rarely seen today due to screening programmes applied in all developed countries and better patient education. Most of the reported cases are highly differentiated carcinomas that present with a delay of more than 12 months [2, 4]. Slow disease progression and absence of distant metastasis in patients suggest low metastasising potential of well-differentiated tumours [11].

Multidisciplinary therapeutic intervention in LABC should be based on staging and imaging techniques such as ultrasonography, computerized tomography, magnetic resonance imaging, axillary and internal mammary lymphoscintigraphy and histopathological assessment of biopsy specimens in order to define the extent of primary and regional tumour involvement [1, 8, 12].

Therapeutic strategies in the treatment of advanced ulcerated breast cancer include surgery, chemotherapy and/or hormonal therapy, radiotherapy (RT), usually supported by therapies aiming to control bleeding and bacterial infection [1, 5, 8]. In all reported methods for hemostasis, such as diathermy, transcatheteral arterial embolization [13] and Argon or CO_2 laser [14], the rate of re-bleeding is high and in most cases the procedure has to be reapplied. Bacterial infection, especially by anaerobes, is the rule in malignant breast ulceration and its control is essential. However most of the reported cases did not develop sepsis with the administration of standard chemotherapeutic doses [5, 6]. Metronidazole gel [15], neomycin/bacitracin solutions [5] and other antibiotic impregnated dressings eliminate malodor and control infection. In all our patients silver-charcoal dressings were used as they are known to effectively control malodour and overgrowth of common infectious agents as well as minimize the risk of bacterial resistance and wound re-bleeding by achieving gentle autolysis and debridement [7, 16]. Furthermore, they regulate the activity of metalloproteinases and provide a moist environment resulting in acceleration of wound healing [7].

Local treatments, including surgery and/or RT have proved to be inadequate therapies for LABC as they do not seem to improve disease-free and overall survival [1, 8, 17]. There is evidence that RT is rather inadequate in ulcerative breast cancer as it is associated with poor rates of ulcer healing or with local recurrence [1, 18]. However, remission rates of 62% have been reported in patients with malignant breast ulceration after hypofractioned RT with 5-FU-radiosensitization [19].

Preoperative chemotherapy has been reported to result in significant reduction of tumour size, and this downstaging allows for breast-conserving surgery in 10-40% of patients [1, 8, 20, 21], though ulceration is considered as an adverse sign for local control of the disease after surgery [22]. Systemic chemotherapy should be coupled with local therapy in order to control local disease, while preventing micrometastasis [1, 8]. Although the optimal chemotherapeutic regimen has not been clearly defined, clinical information suggests that anthracycline-based chemotherapy is the most efficacious [1, 5, 9, 10]. Hormonal therapy also seems to contribute to local and systemic control of the disease and tamoxifen alone has been found to be as efficacious as radiotherapy as initial treatment for Stage III breast cancer [1, 5, 8, 9, 22].

Questions about the optimal sequence of subsequent therapies after primary chemotherapy, in order to achieve better local and systematic control, the role of novel chemotherapeutic agents and new biological therapies (immunotherapy and gene therapy) in LABC [23] still have to be answered by large clinical trials based on the progress of translational research.

Conclusion

There is clinical evidence that the use of chemotherapy coupled with hormonal therapy produces a satisfactory clinical response in ulcerative LABC thus offering prolonged survival and a better quality of life.

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Address reprint requests to:
D. KAKAGIA, Ph.D.
7 P. Kirillou Str.
68100 Alexandroupolis (Greece)