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Short report

Feasibility study of FEC-chemotherapy with dose-intensive epirubicin as initial treatment in high-risk breast cancer

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Summary

Background: The prognosis of patients with stage III B breast carcinoma with metastasis to the apical axillary lymph nodes is poor despite adequate local control achieved by surgery and/or radiation therapy. This study evaluated the feasibility of a dose-intensive up-front chemotherapy regimen in this subgroup of patients.

Patients and methods: A preoperative chemotherapy regimen consisting of 3 courses of fluorouracil 500 mg/m^2, dose-intensive epidoxorubicin 120 mg/m^2 and cyclophosphamide 500 mg/m^2 (DIE-FEC), was administered at 21-day intervals without hematopoietic growth factors to 31 patients with apex-positive disease. All patients were below 60 years of age and none had had prior chemotherapy or radiotherapy.

Results: Seven patients achieved clinical complete responses (23%), and 21 achieved clinical partial responses (68%); three patients had stable disease (10%), one of whom had only ductal carcinoma in situ at histopathologic evaluation, which suggested an additional response to therapy. The major toxicity was moderate bone marrow suppression with a median WBC nadir of 1650/μl (range 500–4600). Other toxic effects were mild.

Conclusion: DIE-FEC is well-tolerated and highly effective as up-front chemotherapy in relatively young patients with high-risk breast cancer, with a 90% (CI 74%–98%) clinical objective response rate.

Key words: breast cancer, epirubicin, pre-operative chemotherapy

Introduction

A combined treatment modality for breast cancer patients with stage IIIB breast cancer with tumor spread to the apical axillary lymph nodes is under development; it incorporates pre-operative chemotherapy followed by surgery and high-dose chemotherapy with autotransplantation. Such an approach would require a highly effective up-front chemotherapy regimen for reducing distant micrometastases that would not compromise the local control rate as a result of surgery or radiotherapy. We investigated the feasibility and efficacy of FEC, with dose-intensive administration of epidoxorubicin (DIE-FEC) [1]. Hematologic growth factors were not used because repeated high-dose chemotherapy with growth factor support could theoretically compromise later attempts to mobilize peripheral hematopoietic stem cells [2].

Patients and methods

Patients

Eligibility criteria included: carcinoma of the breast with apical axillary lymph node metastases at exploration but no distant metastases; age ≤60 years; WHO performance status 0 or 1; adequate renal and hepatic functions, with a creatinine clearance of ≥60 ml/min and a serum bilirubin of ≤25 umol/l. A white blood cell count (WBC) of ≥4.0 × 10^9/l and platelets of ≥100 × 10^9/l were required. A total of 31 patients, with a median age of 45, were entered in this study. Twenty-one of them were premenopausal.

Treatment

The pre-operative chemotherapy regimen consisted of three consecutive courses of fluorouracil 500 mg/m^2, epidoxorubicin 120 mg/m^2 and cyclophosphamide 500 mg/m^2 (DIE-FEC), administered intravenously at 3-week intervals. If the WBC count was 3000/μl or less at day 21, or the platelet count below 100,000/μl, retreatment was delayed for a week. If after 1 week the WBC count was still less than 3000/μl but over 2000/μl, a 50% dose reduction was applied. Anti-emetics consisted of 5 HT-3 antagonists or metoclopramide. A mastectomy or a tumorectomy was performed three to four weeks after the third cycle.

Evaluation of response

The sum of the product of the two largest perpendicular diameters of all measurable lesions (e.g., breast nodule and axillary lymph node) was calculated and used as the parameter indicating tumor response. A partial remission was defined as a ≥50% reduction in size of this sum. A complete response was defined as the disappearance of all detectable lesions. The clinical responses to chemotherapy as judged by physical examination were correlated with the findings at pathological examination of the resected specimens to confirm the chemosensitivity of the primary tumor. Pathologic complete response was defined as no evidence of malignancy at histopathologic examination of the mastectomy specimen.

Results

Responses

In seven patients (23%) a clinical complete response was observed, which in two was confirmed at histo-

pathological examination of the resected specimen. In a third patient, residual carcinoma in situ but no invasive carcinoma was found at microscopy. In the remaining four patients in clinical complete response, microscopic examination of the mastectomy specimen revealed small areas of invasive carcinoma. Partial responses were observed in 21 patients (68%), but in two of these, no residual tumor was found at microscopy of the mastectomy specimen; carcinoma was still present, however, in the resected axillary lymph nodes. Three patients (10%) were considered to have stable disease. One of these, who had presented with a T_3N_1 tumor, had only carcinoma in situ at microscopic evaluation, suggesting an additional response to therapy. Tumor progression was not observed during chemotherapy. There was no obvious relationship between tumor size and clinical response.

Toxicity

Toxicity was expressed in grades according to the WHO criteria [2]. As expected, the main toxic effect of the DIE-FEC regimen was bone marrow suppression (Table 1A). In five patients a one-week treatment delay of the third cycle of chemotherapy was necessary because of neutropenia. Three of them required hospitalization because of neutropenic fever; a *Branhamella catharalis* was cultured from the sputum of one patient. No other positive cultures were obtained. All patients showed rapid recovery after intravenous administration of antibiotics. A brief grade IV thrombocytopenia was observed in a single patient after the third FEC-course; however, platelet transfusions were not necessary.

Gastro-intestinal toxicity consisted mainly of nausea and vomiting despite prophylactic anti-emetic therapy (Table 1B). One patient had grade IV nausea and vomiting during 3 days after the third course; more than 87% of the patients experienced grade II or less. Mucositis was mild, grade I or less, in over 80% of the patients (Table 1B). As expected, complete but reversible (grade III) alopecia was observed in all patients.

Table 1A. Hematologic toxicity expressed as WBC nadir and platelet nadir after each course of chemotherapy.

	FEC_1	FEC_2	FEC_3
Median WBC nadir/μl (range)	1800 (900–3900)	1850 (500–3900)	1650 (500–4600)
Median platelet nadir/μl (range)	151.000 (46–272)	170.000 (39–398)	167.500 (20–319)

Table 1B. Non-hematologic toxicity: Mucositis and nausea/vomiting.

	FEC-1 no. (%)	FEC-2 no. (%)	FEC-3 no. (%)
Mucositis			
Grade: 0	21 (68)	25 (81)	25 (81)
1	4 (13)	– –	2 (6)
2	5 (16)	3 (10)	2 (6)
2–3	1 (3)	1 (3)	1 (3)
3	– –	2 (6)	1 (3)
Nausea/vomiting			
Grade: 0	13 (42)	15 (48)	19 (61)
1	10 (32)	8 (26)	4 (13)
2	5 (16)	4 (13)	4 (13)
3	3 (10)	4 (13)	3 (10)
4	– –	– –	1 (3)

Discussion

The up-front administration of FEC chemotherapy using dose-intensive epidoxorubicin (DIE-FEC) in 31 patients with apex-positive breast cancer resulted in a high objective response rate of 90% (confidence interval 74%–98%), with a clinical complete remission in 23% of cases. Histopathological examination of the breast and the axilla was required for an accurate estimate of the effect of induction chemotherapy.

It appears reasonable to ascribe the high objective response rate to the elevated dose of epirubicin [3]. Despite the high dose of an anthracycline, the degree of bone marrow toxicity was only moderate. To mobilize peripheral stem cells, fourteen patients received a fourth course of DIE-FEC followed by G-CSF after surgery. No excess toxicity was noted and high numbers of peripheral hematopoietic stem cells could be harvested in thirteen patients. In conclusion, three cycles of FEC with dose-intensive epidoxorubicin (DIE-FEC) is highly effective as an up-front chemotherapy regimen in high risk breast cancer patients. It is well-tolerated, has moderate bone marrow suppression as its major toxicity and it does not appear to compromise later stem cell harvesting. The design of the study did not allow any conclusions regarding the duration of response. We believe that DIE-FEC fulfills all the requirements for a pre-operative induction chemotherapy regimen to be used prior to consolidation with very high-dose chemotherapy with autologous peripheral stem cell support.

References

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