Epirubicin or epirubicin and cisplatin as first-line therapy in advanced breast cancer. A phase III study

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Abstract  Purpose: To compare the efficacy and toxicity of epirubicin to that of the combination of epirubicin and cisplatin in patients with advanced breast cancer. Patients and methods: A total of 155 patients were randomized to receive either epirubicin (70 mg/m²) days 1 and 8 every 4 weeks or epirubicin (60 mg/m²) days 1 and 8 plus cisplatin (100 mg/m²) day 1 every 4 weeks. Epirubicin was continued until disease progression or to a cumulative dose of 1000 mg/m². Cisplatin was discontinued after six cycles. In 45 premenopausal women an oophorectomy was performed. None of the evaluable patients had received chemotherapy for metastatic disease. Results: Among evaluable patients (74 in the epirubicin group and 65 in the epirubicin plus cisplatin group) there were 19% vs 29% complete responses, and 42% vs 37% partial responses, with no significant difference. In the epirubicin plus cisplatin group the response rate was significantly higher in previously untreated patients as compared with patients who had received adjuvant chemotherapy (74% vs 55%, P = 0.002). Median times to disease progression were 8.4 months in the epirubicin group and 15.3 months in the epirubicin plus cisplatin group (P = 0.045). Median survival times were 15.1 and 21.5 months, respectively (P = 0.41). In the epirubicin plus cisplatin group leukopenia and thrombocytopenia were significantly more frequent, 29% of the patients developed mild to moderate peripheral neurotoxicity, 34% reported tinnitus and hearing changes, 6 patients developed nephrototoxicity (one died due to nephrotic syndrome), and 3 patients developed leukaemia (two died of this cause).

Congestive heart failure occurred in six patients in the epirubicin group and three patients in the epirubicin plus cisplatin group. Conclusion: Cisplatin plus epirubicin is an active, although highly toxic regimen when used as first-line therapy in advanced breast cancer. The time to disease progression was significantly longer in the cisplatin plus epirubicin group (increased by 82%). Due to toxicity, the combination regimen cannot be recommended. However, the study indicated a very high activity of cisplatin in advanced breast cancer. Studies of first-line therapy in advanced breast cancer including cisplatin or other platin derivatives in combination with, for example, the taxanes are suggested.

Key words  Breast cancer · Cisplatin · Chemotherapy · Epirubicin

Introduction

Cytotoxic chemotherapy is an established modality in the treatment of advanced breast cancer. However, the 5-year survival rate in stage IV breast cancer is still less than 5% [10] and despite intensive efforts, advanced breast cancer remains an incurable disease. Thus, new active drugs and drug combinations must be explored. The anthracyclines, doxorubicin and epirubicin are considered to be two of the most active agents in the treatment of breast cancer [2, 11, 18, 20]. No significant differences in antitumour activity have been found between epirubicin and doxorubicin [2, 18]. A major problem in the clinical use of doxorubicin is the cumulative cardiotoxicity [18]. Of great clinical interest are observations indicating that epirubicin has a lower potential for cardiotoxicity [2, 12, 18, 21].

Despite its wide spectrum of clinical activity, cisplatin initially made little impact in the treatment of advanced breast cancer. There were two main reasons for this. First, early studies usually in heavily pretreated patients suggested little activity (for review, see references 30, 31 and 33). Second, its toxicity spectrum including severe...
emesis and the need for hydration to minimize nephrotoxicity, made it unsuitable compared with established less-complicated regimens (e.g. cyclophosphamide, methotrexate, 5-fluorouracil). However, during recent years data have emerged suggesting that cisplatin used as first-line chemotherapy may be much more active than first thought against breast cancer (for review, see references 30, 31 and 33). Thus, the overall response rate among patients with advanced breast cancer given high-dose cisplatin without prior chemotherapy is 42–54% [13, 15, 19, 32] indicating that cisplatin is among the most active agents in this disease. Cisplatin and anthracyclines appear to have different mechanisms of action and their toxicities only partly overlap. The two compounds might therefore have a synergistic effect, and their use in combination chemotherapy could be of potential clinical benefit.

The primary objective of this phase III study was to compare response rate, time to progression and toxicity of epirubicin as a single agent with those of the combination of epirubicin and cisplatin using maximally tolerable and haematological equitoxic doses in patients with advanced breast cancer. The second objective was to compare survival duration with the two regimens.

Material and methods

Eligibility criteria

Patients with histologically proven, locally advanced or metastatic breast cancer and dimensionally measurable disease were eligible, as were those who had received one prior adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil). Also included were patients with prior endocrine therapy or radiotherapy, either adjuvant or for metastatic disease, up to 4 weeks prior to their inclusion. Further eligibility criteria were: age ≤70 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤3, life expectancy > 3 months, WBC count ≥3000/μl and platelet count ≥100,000/μl, unless due to metastatic bone marrow involvement. Criteria of ineligibility were: evidence of renal disease (serum creatinine > 1.2 mg/dl and/or 51Cr-EDTA clearance < 60 ml/min) or hepatic disease (serum bilirubin > 1.5 mg/dl), brain involvement or leptomeningeal disease, other concomitant cancer, or clinical evidence of cardiac disease defined as congestive heart failure, arrhythmia or a history of myocardial infarction.

Pretreatment evaluation and follow-up

Pretreatment evaluation included a complete history and physical examination, blood cell counts (haemoglobin, WBC, and platelets), serum chemistry profiles (creatinine, calcium, alkaline phosphatase, transaminase, and bilirubin), chest radiography, electrocardiography, 51Cr-EDTA clearance, and bone scans. Areas of increased uptake on bone scans were further evaluated with roentgenograms to determine the nature of the abnormalities. Ultrasound scan of the liver was performed if the serum alkaline phosphatase or transaminases were elevated. Blood cell counts were monitored weekly for the first 8 weeks and thereafter before each treatment and 1 week after treatment. Biochemical profiles were repeated every 4 weeks. In patients receiving cisplatin, 51Cr-EDTA clearance was done every 8 weeks. Evaluable or measurable parameters except bone lesions were reevaluated every second month. Bone lesions were evaluated every third month.

Study design

Informed consent was obtained from all patients, and the study was approved by the regional ethical committee. Consecutive patients were centrally registered and, after stratification for performance status (ECOG 0–1 or 2–3), randomized to either group A (epirubicin 70 mg/m² days 1 and 8 every 4 weeks, regimen A) or group B (epirubicin 60 mg/m² days 1 and 8 plus cisplatin 100 mg/m² day 1 every 4 weeks, regimen B). Epirubicin treatment was continued until disease progression or to a cumulative dose of 1000 mg/m². Cisplatin was discontinued after six cycles. The doses of epirubicin was adjusted according to the WBC and platelet counts on the day of treatment as follows: 100% for WBC counts ≤ 1.5 x 10⁹/μl or platelet counts ≤ 100 x 10³/μl; 50% for WBC counts 2.0–2.9 and/or platelet counts 50–99; 0% for WBC counts < 2.0 and/or platelet counts < 50.

The cisplatin dose was adjusted according to nephrotoxicity as follows: 100% for ⁵¹Cr-EDTA clearance > 60 ml/min; 50% for ⁵¹Cr-EDTA clearance 40–60 ml/min, and 0% for ⁵¹Cr-EDTA clearance < 40 ml/min.

The nadir counts were derived from weekly blood counts. In case of fever due to leukopenia (nadir WBC < 1.5 x 10⁹/μl) and/or bleeding due to thrombocytopenia (nadir platelets < 30 x 10³/μl) in the previous course, the treatment was reinitiated at a dose of 67% of the previous dose.

Epirubicin was supplied by Pharmacia & Upjohn in a powdered form and reconstituted in sterile water (5 mg/ml). The drug was administered by a 5-min infusion through an established intravenous line. Cisplatin was supplied by Bristol-Myers Squibb as a sterile aqueous solution containing 1 mg cisplatin/ml and 9 mg sodium chloride/ml. Treatment consisted of 1000 ml 0.9 N saline isotonic glucose solution over 1.5 h, 500 ml mannitol 20% over 0.5 h followed by cisplatin in 500 ml 0.9 N saline over 0.5 h. As posthydration, 2000 ml 0.9 N saline isotonic glucose was given. All patients receiving cisplatin were hospitalized. The antiemetic regimen consisted of metoclopramide from 60 to 150 mg/day depending on the grade of the emesis.

The response rate to ovulation suppression in premenopausal women with metastatic breast cancer is about 35%. Oophorectomy and ovarian radiation are regarded as equally effective (although rigorous comparative trials have not been completed) [7]. Thus, in premenopausal women an oophorectomy was also performed by irradiation before the start of chemotherapy.

Evaluation of response

Evaluation of response (including response in bone lesions) was done according to WHO criteria [34]. Patients with early death (before 4 weeks) were recorded as having progressive disease. Time to progression was calculated as the time from the first drug administration to progression for both responders and nonresponders. The response duration of complete responders was calculated as time from the date of complete response (CR) to the date of progression, and response duration of partial responders from the time of the start of treatment to progression.

Furthermore, analysis of the results was performed on an “intent to treat” basis and thus all randomized patients were considered evaluable for response, toxicity and survival analysis. None of the patients was lost to follow-up.

Statistical methods

Patient characteristics and responses were compared using Fisher’s exact test or the chi-squared test for categorical variables and t-tests for continuous variables. Confidence limits for differences between response rates were calculated according to the method of Woolf [35]. Survival time and time to disease progression were analysed by Kaplan-Meier estimates [14]. Data from each treatment group were compared by the log-rank test.