Epirubicin/Taxane Combinations in Breast Cancer: Experience From Several Italian Trials

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Doxorubicin/paclitaxel (Taxol) combinations are very active in advanced breast cancer, with objective response rates up to 90%, but have shown a high incidence of cardiotoxicity. A phase I/II trial replacing

Introduction

The anthracyclines and the taxanes have been shown to be the most active single-agent therapies for breast cancer. The incorporation of anthracyclines in combination regimens has increased response rate, remission duration, and survival of patients with advanced disease.[1] Approximately 20% of patients remain disease-free 10 years after achieving a complete response (CR).[2] Moreover, a recently published meta-analysis of adjuvant polychemotherapy showed that anthracycline-containing regimens were moderately superior to non-anthracycline regimens.[3]

The use of anthracyclines is limited, however, by cumulative dose-related cardiotoxicity.[4] Among the possible strategies to decrease this life-threatening toxicity, the development of epirubicin (Ellence), a doxorubicin analog, is of particular interest. Epirubicin retains antitumor activity comparable to that of doxorubicin,[5] but is less cardiotoxic (although it does not eliminate cardiotoxicity) and less myelotoxic than the parent compound at equimolar doses. The need to reduce or avoid cardiac toxicity is evidenced by results of studies of anthracycline/taxane combinations.

Combined Anthracycline/Taxane in Advanced Breast Cancer

The combination of doxorubicin plus paclitaxel (Taxol) proved to be very active as first-line chemotherapy for advanced breast cancer, with an overall response rate of approximately 90% and CR rates as high as 41%.[6,7] The combination of doxorubicin plus paclitaxel, however, was associated with enhanced cardiotoxicity, which became apparent at cumulative doxorubicin doses significantly lower than those recommended when doxorubicin is administered alone or combined with other drugs.[8] Two independent studies by Gianni[9] and Dombernowsky[10] reported a 20% incidence of congestive heart failure (CHF) among metastatic breast cancer patients receiving the doxorubicin plus paclitaxel combination.

Substituting Epirubicin to Ameliorate Cardiac Toxicity

To maintain the high activity of this combination while ameliorating the cardiac toxicity, we have studied an anthracycline/paclitaxel combination that replaced doxorubicin with epirubicin. Study end points were to determine the maximum tolerated dose (MTD) of paclitaxel over 3 hours with a fixed dose of epirubicin, and to evaluate the toxicity and activity in previously untreated metastatic breast cancer patients.

Fifty patients were enrolled in the trial. The MTD was reached with doses of epirubicin at 90 mg/m² plus paclitaxel at 200 mg/m². This combination was found to be feasible, with a low rate of cardiotoxicity (6% incidence of CHF). The overall response rate was 84% and CR rate was 19%.[11-13]

The excellent cardiac tolerability of this combination compared with that associated with
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Doxorubicin/paclitaxel cannot be explained solely based on epirubicin’s lower rate of cardiotoxicity. Another possible explanation may include better patient selection. Moreover, recent data from Gianni and our group showed that coadministration of epirubicin and paclitaxel induces an increase in glucuronidation of epirubicin, leading to increased urinary elimination and decreased plasma levels of epirubicinol, the cardiotoxic metabolite of epirubicin.[14,15]

In contrast, coadministration of doxorubicin with paclitaxel causes nonlinear disposition of doxorubicin, which results in increased plasma concentrations of doxorubicin and its main metabolite doxorubicinol, a major determinant of myocardial damage.[15,16] Thus, the pharmacokinetic interactions of anthracyclines/paclitaxel are different depending on the particular anthracycline used.

Identifying Patients at Risk of Congestive Heart Failure

We conducted a trial of epirubicin plus paclitaxel to evaluate the incidence of clinically significant cardiac toxicity and to identify patients at high risk of developing CHF.[17] We thought it would be particularly important to identify patients for whom the benefits of chemotherapy might be negated by the occurrence of CHF.

In this study of 105 patients with metastatic breast cancer, none developed CHF during the treatment, but nine patients (9%) developed CHF after cumulative epirubicin doses of 1,080 mg/m² (n = 4), 720 mg/m² (n = 2), 630 mg/m² (n = 1), and 540 mg/m² (n = 2). One of the patients who developed CHF after epirubicin cumulative doses of 540 mg/m² had received high-dose consolidation chemotherapy. Median time to manifestation of cardiac symptoms was 3 months after completion of chemotherapy (range: 3 to 6 months).

The incidence of CHF was 13% in patients with pre-existing cardiac risk factors (age, diabetes, hypertension, previous radiotherapy to the chest) and 4% in patients without these risk factors. This analysis showed that the incidence of CHF after epirubicin/paclitaxel treatment is low up to cumulative epirubicin doses of 990 mg/m², thus allowing safe administration of this regimen even in patients who may have received epirubicin in the adjuvant setting. The risk of developing CHF does, however, increase when the cumulative epirubicin dose exceeds 990 mg/m² and when additional cardiac risk factors are present.

Overall, no clear role for the proposed risk factors for cardiotoxicity was observed in this analysis. Nine patients developed CHF, 7 (13%) of 54 patients with and 2 (4%) of 51 patients without risk factors.

Concomitant vs Sequential Epirubicin and Paclitaxel

Based on the pharmacokinetic and pharmacodynamic interactions that occur when anthracyclines and paclitaxel are administered together, we wanted to examine the possibility that combinations of these agents result in subadditive antitumor activity. In a phase III study (MIG 6), concomitant vs sequential administration of epirubicin and paclitaxel are being compared in patients with advanced breast cancer. The primary study end point is overall response rate; secondary end points include CR rates, toxicity, quality of life, pharmacoeconomic, and pharmacokinetic analyses.

To date, 112 patients have been enrolled, all of whom have been evaluated for response. The overall response rate is 60% (CR rate, 13%), with a median progression-free survival of 12.3 months, and a median overall survival of 26.3 months.

Epirubicin Plus Docetaxel as First-Line Chemotherapy

Available data on use of docetaxel (Taxotere) in combination with anthracyclines indicate that this regimen has antitumor activity similar to that of paclitaxel/anthracycline combinations. The rationale for combining epirubicin and docetaxel includes the high level of activity and tolerability of each drug as a single agent, and preliminary evidence suggesting that coadministration of epirubicin and
docetaxel does not result in pharmacokinetic interactions that lead to increased risk of cardiotoxicity.

Based on these data, we are conducting a phase I/II study of epirubicin plus docetaxel as first-line chemotherapy for advanced breast cancer patients. The purpose of the study is to evaluate the MTD of docetaxel in combination with epirubicin at two different dose levels (75 and 90 mg/m²), administered every 21 days to breast cancer patients with locally advanced (LABC) or metastatic (MBC) disease.

At the time of this report, 58 patients (35 LABC and 23 MBC) have been treated and are evaluable for toxicity and response. Grade 4 neutropenia occurred in 69% of cycles, with fever in 11%. Dose-limiting toxicities were febrile neutropenia and grade 4 neutropenia lasting more than 7 days.

The following MTDs have been identified: epirubicin at 90 mg/m² plus docetaxel at 60 mg/m², epirubicin at 75 mg/m² plus docetaxel at 80 mg/m², and epirubicin at 90 mg/m² plus granulocyte-colony colony stimulating factor (G-CSF). The recommended doses for subsequent studies are epirubicin at 75 mg/m²/docetaxel at 80 mg/m² without G-CSF. The overall response rate was 73% (7% complete and 66% partial response.[18]

**Epirubicin Plus Paclitaxel for Early Breast Cancer**

The high level of activity of anthracycline/taxane regimens in patients with metastatic breast cancer has prompted investigations of the role of these regimens in the adjuvant setting.

Italian investigators are performing the Gruppo Oncologico Nord-Ouest (GONO)-MIG 5 multicenter randomized trial in which epirubicin plus paclitaxel (Taxol) (ET) is being compared with fluorouracil, epirubicin, and cyclophosphamide (Cytoxan, Neosar) (FEC) as adjuvant chemotherapy for node-positive breast cancer patients. Because the potential for cardiotoxicity is an important issue in the adjuvant setting, the study includes an analysis of the incidence of CHF.

A total of 631 patients have been evaluated, of whom 314 have received FEC and 317 ET. Follow-up time exceeds 1 year in 92% of patients. Grade 1 (World Health Organization [WHO] criteria) cardiotoxicity was reported in five patients receiving FEC, which occurred from 65 to 127 days after randomization, and in four patients receiving ET, 23 to 29 days after randomization. One patient receiving ET had grade 2 cardiotoxicity after the second chemotherapy course, consisting of sinus block with syncope followed by atrial fibrillation that lasted 24 hours.

Of note, no episodes of CHF were observed among patients receiving the ET combination. In addition to epirubicin’s advantages related to reduced potential for cardiotoxicity, the excellent cardiac tolerability of the adjuvant ET regimen might be related to the low cumulative epirubicin dose (ie, 360 mg/m²) and the good performance status of patients in this trial. However, because epirubicin/paclitaxel combinations have been associated with a low incidence of cardiotoxicity in patients with metastatic breast cancer, the GONO-MIG 5 investigators have recommended continued clinical monitoring during study treatment and follow-up.

**Conclusion and Implications**

The combination of epirubicin and taxanes is feasible and maintains an interesting level of activity. Moreover, cardiotoxicity, which was an important complication of concomitant doxorubicin and paclitaxel treatment, is not a major issue when epirubicin is used instead of doxorubicin. This observation should be considered when planning clinical trials in the adjuvant and neoadjuvant settings.

**References:**


