A Phase II Study of a Dose-Density Regimen With Fluorouracil, Epirubicin, and Cyclophosphamide on Days 1 and 4 Every 14 Days With Filgrastim Support Followed by Weekly Paclitaxel in Women With Primary Breast Cancer

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ABSTRACT

Background. Recent evidence shows that use of anthracycline and taxane adjuvant chemotherapy and dose-dense regimens, consisting of more frequent administration of the drugs, have improved outcomes for breast cancer patients. In this study, we evaluated administration of an epirubicin-based regimen with paclitaxel in a sequential, dose-dense schedule as adjuvant treatment for patients with high-risk primary breast cancer.

Methods. In a phase II Simon two-stage design study, we evaluated the feasibility of a modified fluorouracil, epirubicin, and cyclophosphamide (FEC) regimen at high dose intensity (fluorouracil 500 mg/m² i.v. on days 1 and 4, epirubicin 60 mg/m² i.v. on days 1 and 4, and cyclophosphamide 500 mg/m² i.v. on days 1 and 4; all drugs were administered every 14 days for 3 cycles) with granulocyte colony-stimulating factor support followed by dose-intense weekly paclitaxel 100 mg/m² for 8 cycles. In 11 patients with breast cancer following quadrantectomy ($n = 8$) or modified radical mastectomy ($n = 3$), any grade 3 (G3) or higher nonhematologic toxicity (excluding alopecia, nausea or vomiting, and bone pain, which might be a consequence of the administration of filgrastim) and adherence to the scheduled dose-dense treatment (deliverability) were monitored with the purpose of enrolling an additional 27 patients in the case of a satisfying toxicity profile and deliverability of the planned treatment (at least 7 patients completing the treatment).

Results. Five of 11 patients experienced G3 or higher nonhematologic toxicity during the FEC regimen. We did not

observe G3 or higher nonhematologic toxicity related to paclitaxel treatment. In particular, three patients experienced G3 fatigue, one patient had G3 oral mucositis, three patients had G3 hypokalemia, one patient had G3 syncope, one patient had G3 transaminitis (alanine aminotransferase), one patient experienced G4 pulmonary thromboembolism, and 1 patient had a G3 breast infection. Four of 11 patients received the regimen with a 25% dose reduction of day 1 and 4 administrations of FEC. Seven of 11 patients required FEC delay ≥ 7 days in at least 1 cycle, regardless of dose intensity. Two patients failed to complete the FEC regimen. Two of the remaining 9 patients were treated with paclitaxel delay ≥ 7 days in at least one cycle. After a median follow-up of 28 months, 9 patients were continuously disease free.

Conclusion. The tolerability rate of a dose-dense regimen with FEC followed by weekly paclitaxel was considered not promising for completing the accrual of this study. *The Oncologist* 2015;20:239–240

DISCUSSION

Dose-dense chemotherapy, in which standard-dose chemotherapy is delivered with shorter intervals between the cycles, can be considered a treatment option for high-risk early breast cancer [1]. It is well established that an anthracycline-based regimen improves outcome of early stage breast patients compared with cyclophosphamide, methotrexate, and fluorouracil and that better results are reached adding taxanes to

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an anthracycline-based regimen [5]. Citron et al. showed improved clinical outcome using a dose-dense schedule of a combination of doxorubicin, cyclophosphamide, and paclitaxel compared with a conventional schedule [7].

Our study enrolled high-risk breast cancer patients with >4 positive axillary nodes or patients without positive axillary nodes or <4 positive nodes but tumor size >1 cm and ≥ 2 of the following features: histological grade 3, Ki-67 >30%, estrogen receptor (ER) negative, or presence of lymphovascular invasion. We modified the FEC regimen to obtain an epirubicin-intensive dose-dense scheme with support of granulocyte colony-stimulating factor (G-CSF). We planned 3 cycles of FEC to administer epirubicin with a cumulative dose of 360 mg/m², significantly below the maximum safe cumulative dose. This was followed by weekly paclitaxel 100 mg/m² for 8 cycles, the maximum tolerated dose found in a phase I study with manageable toxicity when sequentially associated with an anthracycline-based chemotherapy [13]. In the first stage, we evaluated the percentage of the 11 planned patients who completed the first 3 cycles of therapy with satisfying toxicity profiles and dose density of the planned treatment (needed at least 7 patients; i.e., 63.6% to define the study as having a promising outcome), with the purpose of enrolling 27 additional patients in the second stage.

In the first analysis, 5 of 11 patients (54.5%) experienced G3 or higher nonhematologic toxicity during treatment with the FEC regimen (Fig. 1). Four of 11 patients received a 25% dose reduction of the day 1 and 4 administrations of FEC. Seven of 11 patients were required FEC delay ≥ 7 days in at least 1 cycle, regardless of dose intensity. Two patients failed to complete the FEC regimen because of prolonged treatment delay in one case and because of distant recurrence in the other. Febrile

Figure 1. Kaplan-Meier curve showing the adverse event-free survival estimate: survival without occurrence of any grade 3 or higher nonhematologic toxicity.

neutropenia was observed in six patients despite G-CSF support with subsequent hospitalization, and G3 anemia required blood transfusion in one patient. No significant cardiac toxicity occurred.

In conclusion, the tolerability rate of a dose-dense regimen with FEC followed by weekly paclitaxel was considered not promising for completing the accrual of this study, even with a good cardiac safety profile. Moreover, the management of dose-dense toxicity, necessary hospitalization for febrile neutropenia, and/or G3 or higher other hematologic and non-hematologic toxicities failed to ensure good quality of life, as is expected in an adjuvant-regimen setting.

Author disclosures and references available online.