Dose-Dense FEC Followed by Dose-Dense Ixabepilone as Neoadjuvant Treatment for Breast Cancer Patients: A Feasibility Study

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ABSTRACT

Background. Ixabepilone is an effective chemotherapy in metastatic breast cancer that has been pretreated with anthracyclines and is resistant or refractory to taxanes. Adjuvant dose-dense (DD) chemotherapy is more effective than regimens administered every 3 weeks, especially in hormonal receptor (HR)-negative tumors.

Methods. A feasibility study of neoadjuvant DD ixabepilone was conducted in breast cancer patients with tumors measuring at least 2 cm. Patients received 5-fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m² ("FEC" in combination) administered intravenously on day 1 every 14 days with granulocyte-colony stimulating factor (filgrastim) followed by ixabepilone 40 mg/m² administered intravenously on day 1 every 14 days with granulocyte-colony stimulating factor. The study's primary endpoint was feasibility, and the secondary endpoint was pathologic complete response. A two-stage Simon's design was adopted.

Results. Forty-seven patients were enrolled, and 42 were evaluable. For 10 of 42 patients, DD ixabepilone was not feasible. Six (14%) required ixabepilone interruption, and four (9.5%) required ixabepilone dose reduction of 25%. One toxic death occurred. Hematologic grade 3–4 toxicities included anemia (9.5%), grade 4 neutropenia (2.4%), febrile neutropenia (4.8%), and thrombocytopenia (2.4%). Nonhematologic grade 3–4 toxicities consisted of fatigue (14.3%), mucositis (14.3%), sensory neuropathy (7.1%), onychopathy (7.1%), and liver toxicity (4.8%). Grade 2 sensory neuropathy lasting longer than 7 days was recorded in 11.9% of patients. Pathologic complete response was observed in 16 of 42 patients (38.1%),

including 11 of 23 (47.8%) with HR-negative tumors and 5 of 19 (26.3%) with HR-positive tumors.

Conclusion. Despite high activity, DD ixabepilone after DD FEC is poorly tolerated. *The Oncologist* 2013;18:924–925

DISCUSSION

Ixabepilone, a semisynthetic epothilone B analog, is a chemotherapeutic drug belonging to the epothilone class of agents. In vitro, ixabepilone demonstrated low susceptibility to multiple tumor resistance mechanisms, including efflux transporters, β -tubulin mutations, and β III overexpression, and showed tubulin polymerization potency 2.5 times more potent than paclitaxel [1].

In phase I studies, maximum tolerated doses of ixabepilone were 6 mg/m² intravenously from day 1 to day 5 every 3 weeks [2], 8 mg/m² intravenously from day 1 to day 3 every 3 weeks [3], and 40 and 50 mg/m² intravenously on day 1 every 3 weeks [4–6]. Dose-limiting toxicities included febrile neutropenia, grade 3–4 neutropenia, mucositis, fatigue, ileus, myalgia, and arthralgia. In phase II trials, ixabepilone every 3 weeks was administered to patients who were pretreated with anthracyclines and/or were resistant or refractory to taxanes, obtaining response rates (RRs) of 12%–42% [7–10]. Of note, in patients defined as resistant to taxanes, RRs ranged from 12% to 19%. In two phase III studies, ixabepilone added to capecitabine compared with capecitabine alone in metastatic breast cancer resistant or refractory to taxanes improved progression-free survival by a statistically significant 1.6–2.0 months and increased the RR by 14%–21% but did not significantly prolong overall survival [11–13]. In four large randomized trials, dose-dense (DD) adjuvant chemotherapy im-

ClinicalTrials.gov Identifier: NCT00751868

Sponsors: Independent clinical research; Bristol-Myers Squibb (ixabepilone supply); Clinical Research Technology (data collection)

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IRB Approved: Yes

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proved disease-free survival [14–18] and sometimes overall survival [16] compared with chemotherapy administered every 3 weeks.

Our study is the first to test the feasibility of DD ixabepilone. DD ixabepilone after DD 5-fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m² (known as “FEC” in combination) was associated with toxicity higher than was prespecified as acceptable: 14% of patients required ixabepilone interruption, and 9.5% required a 25% dose reduction. One toxic death occurred because of multiorgan failure. Hematologic grade 3–4 toxicities included anemia (9.5%) and febrile neutropenia (4.8%). Nonhematologic grade 3–4 toxicities consisted of fatigue (14.3%), mucositis (14.3%), sensory neuropathy (7.1%), onychopathy (7.1%), liver toxicity (4.8%), and myalgia (4.8%). Grade 2 sensory neuropathy lasting longer than 7 days occurred in 11.9% of patients. Details about dose reduction or interruption leading to nonfeasibility of ixabepilone are listed in Table 1.

There are other examples of nonfeasibility of DD chemotherapy including taxanes. Full DD docetaxel (i.e., 100 mg/m² every 2 weeks with granulocyte-colony stimulating factor support) is associated with a high incidence of grade 3–4 toxicities, most notably hand and foot syndrome [19–21]. In addition, higher toxicity and more frequent dose reductions were observed when DD docetaxel was administered at full doses before rather than after an anthracycline [22]. Unlike ixabepilone and docetaxel, paclitaxel is a taxane that can be administered at a full DD schedule (i.e., 175–225 mg/m² every 2 weeks with granulocyte-colony stimulating factor support) [15–17]. In terms of activity, we achieved a pathologic complete RR of 38.1% (47.8% in hormonal receptor [HR]-negative tumors and 26.3% in HR-positive tumors), confirming previ-

Table 1. Toxicities requiring interruption or dose reduction of ixabepilone (reasons for nonfeasibility)

Patient no.	Toxicity	Dose reduction or interruption of ixabepilone
6	Grade 2 sensory neuropathy >7 days	– 25% cycles 2, 3, and 4
10	Grade 3 mucositis Grade 3 onychopathy	Interruption
11	Grade 3 sensory neuropathy Grade 3 mucositis	– 25% cycle 2
13	Grade 4 neutropenia	– 25% cycle 3
22	Febrile neutropenia Grade 3 mucositis	Interruption
27	Toxic death	Interruption
32	Grade 3 liver toxicity	Interruption
42	Grade 2 sensory neuropathy >7 days	– 25% cycles 3 and 4
43	Grade 2 sensory neuropathy >7 days	Interruption
44	Grade 3 mucositis Grade 3 fatigue Grade 3 sensory neuropathy	Interruption

ous findings of Baselga et al. showing that monotherapy with ixabepilone every 3 weeks was associated with a pathologic complete RR of 18% in an unselected population and 29% among patients with HR-negative tumors [23].

DISCLOSURES

Author disclosures and references are available online.