BRIEF REPORT

Life-Threatening Sepsis Associated With Adjuvant Doxorubicin Plus Docetaxel for Intermediate-Risk Breast Cancer

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ANTHRACYCLINES ARE AMONG the most widely used agents for breast cancer treatment, followed by taxanes, which were gradually introduced during the last decade. Combinations of these drug classes have proven superior to anthracyclines alone in advanced or metastatic breast cancer,1,2 while taxanes are still under evaluation in early breast cancer.3 Uncertainties regarding the optimal schedule of administration in combination with anthracyclines, as well as safety and cost issues, are fueling a debate on whether the use of taxanes is justified outside of clinical trials.4

Several groups have tested combinations of docetaxel with anthracyclines in adjuvant and neoadjuvant settings, and the data were recently reviewed.3 Higher rates of febrile neutropenia are reported with these combinations, than with more traditional

Context Adjuvant chemotherapy with new cytotoxic agents for breast cancer must be properly assessed for toxicity.

Objective To describe adverse events associated with adjuvant chemotherapy for breast cancer, which led to premature termination of a clinical trial.

Design, Setting, and Patients We conducted a prospective randomized multicenter study (Reposant sur des Arguments Pronostiques et Prédicifs [RAPP]-01) to compare the effectiveness of 2 chemotherapy regimens. Patients (women aged 18-70 years) had primary unilateral breast cancer and either a moderate number of positive axillary lymph nodes (≤3) or no positive axillary lymph nodes (NO), but were at a high risk of relapse. Patients were treated at 11 French cancer referral centers from June 1999 through January 2003. Primary prophylaxis for febrile neutropenia was not recommended in the study protocol.

Interventions Doxorubicin, 50 mg/m², plus docetaxel, 75 mg/m², or doxorubicin, 60 mg/m², plus cyclophosphamide, 600 mg/m², given postoperatively for 4 courses.

Main Outcome Measures The main end point was the disease-free survival rate at 5 years, as estimated using the Kaplan-Meier product limit method. Secondary end points included safety, which is the focus of this article, and overall survival.

Results A total of 627 women were enrolled. Median follow-up is currently too short (24 months) to analyze the primary end point. The trial was terminated prematurely when 2 deaths related to drug toxicity and 1 case of perforative peritonitis occurred among patients with febrile neutropenia, all in the doxorubicin-docetaxel group. The incidence of febrile neutropenia was significantly higher with the doxorubicin-docetaxel regimen (40.8%) than with the doxorubicin-cyclophosphamide regimen (7.1%) (P<.001).

Conclusions A high risk of life-threatening complications associated with the doxorubicin-docetaxel regimen was found in this open-label controlled trial. The doxorubicin-docetaxel combination should not be considered as an alternative to the doxorubicin-cyclophosphamide regimen outside carefully designed studies that include primary prophylaxis for febrile neutropenia.

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regimens incorporating only anthracyclines. In the Breast Cancer International Research Group (BCIRG) 001 trial, a combination of docetaxel, 75 mg/m², with doxorubicin and cyclophosphamide caused febrile neutropenia in 23.9% of patients, compared with 2.4% of patients treated with 5-fluorouracil, doxorubicin, and cyclophosphamide. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial, 21.2% of patients developed febrile neutropenia when docetaxel was administered sequentially at 100 mg/m², following anthracyclines and cyclophosphamide, compared with 7.3% of patients when docetaxel was not included in the treatment. These rates are lower than the 40% threshold quoted in international guidelines warranting the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis. Here we report the occurrence of 3 serious adverse events, all associated with febrile neutropenia and resulting in 2 deaths, during a French multicenter trial of adjuvant chemotherapy comparing anthracyclines plus cyclophosphamide vs anthracyclines plus docetaxel in women with early stage breast cancer (Reposant sur des Arguments Pronostiques et Prédictifs [RAPP]-01 trial). These events led to premature termination of the trial.

METHODS

Eligible patients were women aged between 18 and 70 years recruited in 11 French cancer referral centers who had unilateral operable breast cancer with clear surgical margins and axillary node clearance, and who were classified as having high-risk node-negative (N0) or limited node-positive (N+ ≤3) disease. Written informed consent was required. High-risk N0 status was defined according to the Saint-Gallen consensus statement. Central randomization was performed by fax or telephone in the Biostatistics Department of René Huguenin Cancer Center (Saint-Cloud, France), which guaranteed allocation concealment. It was stratified according to the participating center, node status (N0 vs N+), and proliferation (Ki67 antigen, <25% vs ≥25%), using a computerized random-number generator.

The patients were randomly assigned to receive 4 postoperative cycles of doxorubicin, 50 mg/m², plus docetaxel, 75 mg/m² (recommended dose determined in a phase 1 study) or 4 postoperative cycles of doxorubicin, 60 mg/m², plus cyclophosphamide, 600 mg/m². The latter regimen is a well-established reference schedule of anthracycline-based chemotherapy. In keeping with international guidelines, chemotherapy was delivered every 3 weeks without primary G-CSF prophylaxis. Use of G-CSF was recommended only for grade 3 or 4 febrile neutropenia with a temperature exceeding 38°C and requiring oral or intravenous antibiotics (National Cancer Institute Common Toxicity Criteria). The primary end point was the disease-free survival rate at 5 years. To be able to detect a difference in 5-year disease-free survival of 10% (70% to 80%) with a 1-sided type I error of 5% and a power of 90%, we planned to recruit 700 patients (350 per group) over 36 months. There were no stopping rules and no scheduled interim analysis. Toxicity frequencies were compared by using the χ² test. P<.05 was considered significant. The steering committee was in charge of study supervision, monitoring accrual, treatment compliance, and safety. The protocol was approved by the institutional review board of each participating center and by the study ethics review committee.

RESULTS

Conduct of the Study

Enrollments started in June 1999. In March 2000, after inclusion of 45 patients in the doxorubicin-docetaxel group, a 49-year-old patient with N0 disease and no history of functional gastrointestinal disease developed latent abdominal pain on day 7 after a first cycle of doxorubicin-docetaxel, followed within 48 hours by intestinal obstruction, febrile neutropenia, and suspected mesenteric infarction resulting in death. Autopsy was not performed. The steering committee did not consider this serious adverse event as specifically attributable to the taxane-based study regimen and decided that enrollments could continue.

In January 2001, after inclusion of 150 patients in the doxorubicin-docetaxel group, a second case of febrile neutropenia with gastrointestinal disorders occurred in a 34-year-old woman with N+ disease and no history of abdominal complaints. She developed perforative peritonitis and septic shock 6 days after her fourth cycle of doxorubicin-docetaxel. She recovered after extensive intestinal surgery, which showed diverticulosis, and spent 3 weeks in intensive care. Enrollments were adjourned pending a survey of similar serious adverse events in other trials of docetaxel (ongoing or closed to inclusions) and in the Aventis database. The survey failed to identify factors explaining the higher incidence of these events in our trial. The written information and consent forms were modified to mention a potential risk of gastrointestinal disorders and the ethics committee, independent data monitoring committee, and the French Medicines Agency authorized enrollments to proceed in July 2001.

In January 2003, after enrollment of 311 patients in the doxorubicin-docetaxel group, a third case of febrile neutropenia with gastrointestinal disorders occurred after a first cycle of doxorubicin-docetaxel in a 39-year-old patient with N+ disease. She had a history of nonactive mild diverticulosis and colonoscopic rectal polyph excision. She developed latent abdominal pain on day 6 and died on day 13 with septic shock and multorgan failure, Pseudomonas aeruginosa septicemia, and diarrhea. Autopsy revealed sigmoiditis with diverticulitis, partial perforation of the mesocolon, and local perforation. The steering committee terminated the study in January 2003, with 627 patients enrolled, because of the unexpectedly high toxic mortality rate (2/311 or 0.63%). The 18 patients...
still receiving doxorubicin-docetaxel were switched to doxorubicin-cyclophosphamide.

**Characteristics, Safety Results, and Adverse Event Investigations**

The patients’ characteristics were well balanced between the 2 treatment groups (Table 1). In the doxorubicin-docetaxel group, however, we found a higher rate of febrile neutropenia (40.8% vs 7.1% per patient, P < .001; 14.0% vs 1.9% per cycle, P < .001), more frequent G-CSF use, more frequent dose reductions, and fewer delayed treatment cycles (Table 2). Among patients with grade 3 or 4 gastrointestinal toxicity, there was less nausea and vomiting, more diarrhea, and more mucositis in the doxorubicin-docetaxel group (Table 3). The doxorubicin-docetaxel regimen was associated with more amenorrhea than the doxorubicin-cyclophosphamide regimen (77.4% vs 54.7%, P < .001). No grade 3 or 4 docetaxel-specific adverse events, defined as severe fluid retention or nail disorders, were observed.

Of the 87 severe adverse events reported to the French Medicines Agency, 72 (82.8%) occurred in the doxorubicin-docetaxel group, of which 87.5% were associated with febrile neutropenia (Table 2). Treatment was completed as planned in the 316 patients assigned to the doxorubicin-cyclophosphamide group, while treatment was discontinued prematurely in 17 patients in the doxorubicin-docetaxel group (5.5%) because of adverse events (11 patients) or patient refusal to continue therapy (6 patients).

**COMMENT**

Although the 3 severe adverse events described herein did not correspond to typhilitis or neutropenic enterocolitis sometimes observed with use of docetaxel,13,14 1 patient required extensive intestinal surgery, 2 patients died, and all 3 cases were associated with febrile neutropenia.

Rare cases of toxic death (0.2%-0.3%) have been reported with various schedules of adjuvant chemotherapy such as doxorubicin-cyclophosphamide and combination regimens of cyclophosphamide, methotrexate, and 5-fluorouracil in multicenter trials conducted in the 1980s and early 1990s.15 However, acute toxic deaths were generally due to cardiac disorders, even in the absence of anthracycline use, as in the cyclophosphamide, methotrexate, and 5-fluorouracil group of the NSABP B-23 trial.15 The rate of toxic death has decreased far below 0.10% in more recent trials, with high-dose epirubicin-based adjuvant therapy for example.16 We observed a much higher rate of toxic death (0.63%) with the doxorubicin-docetaxel regimen. The higher rate of febrile neutropenia observed with doxorubicin-docetaxel than with doxorubicin-cyclophosphamide in our trial (40.8% vs 7.1%) may have induced severe immunosuppression and

### Table 1. Characteristics of Early Stage Breast Cancer Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Doxorubicin-Docetaxel (n = 311)</th>
<th>Doxorubicin-Cyclophosphamide (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>53 (27-70)</td>
<td>52 (26-70)</td>
</tr>
<tr>
<td>WHO performance scale score = 0, No. (%)</td>
<td>277 (89.1)</td>
<td>283 (89.6)</td>
</tr>
<tr>
<td>Prenomenopausal, No. (%)</td>
<td>146 (46.9)</td>
<td>150 (47.5)</td>
</tr>
<tr>
<td>Conservative breast surgery, No. (%)</td>
<td>223 (71.7)</td>
<td>226 (71.5)</td>
</tr>
<tr>
<td>Ductal carcinoma, No. (%)</td>
<td>253 (81.4)</td>
<td>255 (80.7)</td>
</tr>
<tr>
<td>In situ component</td>
<td>195 (62.7)</td>
<td>190 (60.1)</td>
</tr>
<tr>
<td>Nodal status, No. (%)</td>
<td>131 (42.1)</td>
<td>139 (44.0)</td>
</tr>
<tr>
<td>Tumor size, median (range), mm</td>
<td>20 (6-80)</td>
<td>20 (3-80)</td>
</tr>
<tr>
<td>Histological grading (SBPR), No. (%)</td>
<td>63 (20.4)</td>
<td>39 (12.6)</td>
</tr>
<tr>
<td>II</td>
<td>139 (45.0)</td>
<td>147 (47.6)</td>
</tr>
<tr>
<td>III</td>
<td>107 (34.7)</td>
<td>123 (39.8)</td>
</tr>
<tr>
<td>Not available</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Hormone receptor positive, No. (%)</td>
<td>250 (80.4)</td>
<td>257 (81.3)</td>
</tr>
<tr>
<td>K67 antigen ≥25%</td>
<td>135 (43.4)</td>
<td>140 (44.3)</td>
</tr>
<tr>
<td>HER2 + + +</td>
<td>34 (10.8)</td>
<td>38 (12.0)</td>
</tr>
</tbody>
</table>

Abbreviations: HER2, human epidermal growth factor receptor 2; SBPR, Scarff, Bloom, and Richardson grade; WHO, World Health Organization.

*Estrogen receptor or progesterone receptor positive.

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### Table 2. Hematological Toxicity

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>Patients, No. (%)</th>
<th></th>
<th>Cycles, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doxorubicin-Docetaxel (n = 311)</td>
<td>Doxorubicin-Cyclophosphamide (n = 316)</td>
<td>P Value</td>
<td>Doxorubicin-Docetaxel (n = 1233)</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>126 (40.8)</td>
<td>22 (7.1)</td>
<td>&lt;.001</td>
<td>168 (14.0)</td>
</tr>
<tr>
<td>Use of G-CSF†</td>
<td>115 (37.6)</td>
<td>27 (8.7)</td>
<td>&lt;.001</td>
<td>276 (30.3)</td>
</tr>
<tr>
<td>Delayed cycles‡</td>
<td>21 (6.9)</td>
<td>51 (16.3)</td>
<td>&lt;.001</td>
<td>22 (2.4)</td>
</tr>
<tr>
<td>Dose reduction ≥20%‡</td>
<td>12 (3.9)</td>
<td>4 (1.3)</td>
<td>.04</td>
<td>18 (2.0)</td>
</tr>
</tbody>
</table>

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

*Febrile neutropenia defined as any grade 3 or 4 neutropenia plus fever (temperature ≥38°C) requiring antibiotics; no systematic weekly blood counts; control mandatory on day 21.
†Primary antibiotic or G-CSF prophylaxis not permitted; G-CSF recommended only after an episode of febrile neutropenia plus dose reduction if another episode occurred.
‡For reasons of hematological toxicity.
contributed to the high rate of toxic death, which was 3 times as much as that observed in the NSABP B-27 trial, in which 3 of 7 deaths were attributable to sequential docetaxel immunosuppression among 1584 patients (0.19%).

The Spanish GEICAM Group reported that primary G-CSF prophylaxis reduced the rate of febrile neutropenia induced by adjuvant doxorubicin-docetaxel-cyclophosphamide therapy from 23.8% to 3.5% and halved the rate of grade 3 or 4 toxicity (50.4% vs 20%). Likewise, in the BCIRG-004 trial, prophylactic use of growth factors during the doxorubicin-docetaxel-cyclophosphamide regimen reduced the rate of febrile neutropenia to 7%. The 40% incidence of febrile neutropenia in our study is alarmingly high and indicates an unacceptable toxicity profile. It warrants the use of primary G-CSF prophylaxis, in accordance with international guidelines.

Table 3. Gastrointestinal Toxicity

<table>
<thead>
<tr>
<th>Type of Toxicity and Grade</th>
<th>Doxorubicin-Docetaxel (n = 311)</th>
<th>Doxorubicin-Cyclophosphamide (n = 316)</th>
<th>P Value</th>
<th>Doxorubicin-Docetaxel (n = 1233)</th>
<th>Doxorubicin-Cyclophosphamide (n = 1264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting 0-2</td>
<td>294 (94.5)</td>
<td>285 (90.5)</td>
<td>.05</td>
<td>1175 (98.3)</td>
<td>1188 (96.7)</td>
<td>.009</td>
</tr>
<tr>
<td>3-4</td>
<td>17 (5.5)</td>
<td>30 (9.5)</td>
<td></td>
<td>20 (1.7)</td>
<td>41 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea 0-2</td>
<td>302 (97.1)</td>
<td>313 (99.4)</td>
<td>.03</td>
<td>1186 (99.2)</td>
<td>1227 (99.8)</td>
<td>.03</td>
</tr>
<tr>
<td>3-4</td>
<td>9 (2.9)</td>
<td>2 (0.6)</td>
<td></td>
<td>9 (0.8)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Mucositis 0-2</td>
<td>296 (95.2)</td>
<td>309 (98.0)</td>
<td>.04</td>
<td>1180 (98.7)</td>
<td>1223 (99.5)</td>
<td>.04</td>
</tr>
<tr>
<td>3-4</td>
<td>15 (4.8)</td>
<td>6 (2.0)</td>
<td></td>
<td>15 (1.3)</td>
<td>6 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain 0-2</td>
<td>297 (96.5)</td>
<td>309 (98.0)</td>
<td>.06</td>
<td>1181 (98.8)</td>
<td>1223 (99.5)</td>
<td>.06</td>
</tr>
<tr>
<td>3-4</td>
<td>14 (4.5)</td>
<td>6 (2.0)</td>
<td></td>
<td>14 (1.2)</td>
<td>6 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Grades based on National Cancer Institute Common Toxicity Criteria version 2.0. 0 indicates no adverse event or within normal limits; 1 = mild adverse event; 2 = moderate adverse event; 3 = severe and undesirable adverse event; 4 = life-threatening or disabling adverse event; and 5 = death related to adverse event.

Table 4. Declared Serious Adverse Events

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Doxorubicin-Docetaxel (n = 311)</th>
<th>Doxorubicin-Cyclophosphamide (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With febrile neutropenia</td>
<td>63 (20.3)</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td>Plus death</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Plus intestinal surgery</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Without febrile neutropenia</td>
<td>9 (2.9)</td>
<td>7 (2.2)</td>
</tr>
</tbody>
</table>

The comparison between groups of total number of serious adverse events was significant (P<.001).

The prevalence of diverticulosis increases with age from less than 10% in persons younger than 40 years to 50% to 66% in those 80 years and older. There is no clear difference in prevalence between the general population and patients with breast cancer, but the precise frequency is difficult to measure because most patients are asymptomatic or present with nonspecific abdominal symptoms such as constipation and abdominal pain.

Of note, the second and third serious adverse events described herein occurred in patients with either occult or previously uncomplicated diverticulosis. The prevalence of diverticulosis increases with age from less than 10% in persons younger than 40 years to 50% to 66% in those 80 years and older. There is no clear difference in prevalence between the general population and patients with breast cancer, but the precise frequency is difficult to measure because most patients are asymptomatic or present with nonspecific abdominal symptoms such as constipation and abdominal pain.

Although our trial suggests a possible link between preexisting diverticulosis and the onset of these life-threatening complications, no such relation was found in large series of similar cases studied in a single institution. In our trial, randomization should, in principle, have led to a similar prevalence of diverticulosis in the 2 groups. Because routine colonoscopic screening is not feasible in this setting, patients selected to receive regimens like doxorubicin-docetaxel should have a thorough history-taking, and general practitioners must be trained to rapidly diagnose these events, bearing in mind that signs and symptoms of diverticulitis are often more subtle in immunosuppressed patients than in immunocompetent persons.

Patients with compatible symptoms must be referred to a specialist for vigorous supportive care.
Although encouraging results in similar adjuvant trials support the routine use of taxanes as a component of standard therapy for node-positive breast cancer patients, the possibility that more intensive anthracycline-containing regimens might produce similar results cannot be excluded. High-risk node-negative patients can have a poorer prognosis than patients with limited node involvement, and one might be also tempted to use taxane-based regimens for them too, despite the lack of recommendations based on phase 3 clinical trials.

In conclusion, this study shows that the doxorubicin-docetaxel combination is associated with an increased risk of severe sepsis and life-threatening complications. Clinicians should be aware of the potential toxicity of the doxorubicin-docetaxel regimen and consider the preventive use of G-CSF and/or antibiotics (neither of which was recommended at the time of our trial) in both the adjuvant and metastatic settings. At this time the doxorubicin-docetaxel regimen should not be recommended outside of carefully designed clinical trials.

Author Contributions: Dr Brain, as principal investigator, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brain, Extra, Combe, Noguès, Roussé. Acquisition of data: Brain, Bachelot, Serin, Kirschner, Graic, Eymard, Roussé. Analysis and interpretation of data: Brain, Bachelot, Eymard, Extra, Combe, Noguès, Roussé, Fourme. Drafting of the manuscript: Brain, Serin, Graic, Extra, Combe, Roussé.

Critical revision of the manuscript for important intellectual content: Brain, Bachelot, Serin, Kirschner, Eymard, Extra, Combe, Noguès, Roussé, Fourme. Statistical analysis: Brain, Extra, Combe, Noguès, Roussé, Fourme. Obtained funding: Brain, Combe, Roussé. Administrative, technical, or material support: Roussé. Study supervision: Brain, Serin, Extra, Combe, Roussé.

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