First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: a multicenter, randomized, phase III study

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Background: This randomized, phase III study compared the efficacy and safety of first-line gemcitabine versus epirubicin in the treatment of postmenopausal women with metastatic breast cancer (MBC).

Patients and methods: Patients aged ≥ 60 years (median 68 years) with clinically measurable MBC received either gemcitabine 1200 mg/m² or epirubicin 35 mg/m² on days 1, 8, and 15 of a 28-day cycle.

Results: Of 410 patients entered, 397 (198 gemcitabine and 199 epirubicin) were randomized and qualified for the time to progressive disease (TTP) and survival analyses. Total cycles administered in 185 gemcitabine and 192 epirubicin patients, respectively, were 699 (mean 3.5, range 0–12) and 917 (mean 4.6, range 0–10). Epirubicin demonstrated statistically significant superiority in TTP (6.1 and 3.4 months, \( P = 0.0001 \)), overall survival (19.1 and 11.8 months, \( P = 0.0004 \)), and independently assessed response rate (40.3% and 16.4% in 186 and 183 evaluable patients, \( P < 0.001 \)). For gemcitabine (n = 190) and epirubicin (n = 192), respectively, common WHO grade 3/4 toxicities were neutropenia (25.3% and 17.9%) and leukopenia (14.3% and 19.3%). Of the 28 on-study deaths (17 gemcitabine, 11 epirubicin), three were considered possibly or probably related to treatment (gemcitabine).

Conclusions: Postmenopausal women ≥60 years of age with MBC tolerate chemotherapy well. In this study, epirubicin was superior to gemcitabine in the treatment of MBC in women age ≥60, confirming that anthracyclines remain important drugs for first-line treatment of MBC.

Key words: elderly patients, epirubicin, gemcitabine, metastatic breast cancer

Introduction

Breast cancer is one of the most common cancers, and a leading cause of cancer death in women [1, 2]. Among women with breast cancer in Western countries, 30%–40% have metastatic disease [3]. Because there are few long-term survivors among patients with metastatic breast cancer (MBC), the major goals of therapy include a longer time to progressive disease (TTP) and better symptom relief without increasing toxicity or compromising quality of life [4, 5].

Breast cancer is one of the five leading causes of cancer death in women aged 65 and older [6]. In fact, age is identified as a common risk factor for the development of breast cancer and other epithelial cancers [1]. In postmenopausal, elderly patients, the treatment of choice is endocrine therapy; however, chemotherapy is generally preferred in patients who have hormone-receptor negative tumors, who do not respond to or have progressed despite endocrine therapy, or who have visceral and rapidly progressive systemic disease [7].

The most effective chemotherapeutic agents for the treatment of MBC include anthracyclines (doxorubicin and epirubicin) and the taxanes (docetaxel and paclitaxel) [4, 5, 8, 9]. Epirubicin is used widely in the treatment of breast cancer, and is one of the most active regimens in the adjuvant or metastatic setting [10–12]. Various doses and schedules of epirubicin have been investigated and Bastholt demonstrated that 90 mg/m² every 3 weeks was the optimal dose for epirubicin [13]. However, several studies have consistently demonstrated that low-dose anthracyclines may be equally effective, but significantly less toxic, if administered on
a weekly schedule rather than the conventional 3-week schedule [14–17].

Few cancer treatment trials, however, have adequately addressed the elderly population [6, 18]. In a National Cancer Institute (NCI) analysis comparing SEER (Surveillance, Epidemiology and End Results) incidence and NCI accrual rates, only 17.3% of women enrolled in breast cancer trials were 65 years or older, in contrast to the fact that this age group constitutes 47.7% of all breast cancer cases [18]. Moreover, the likelihood of not treating a patient, especially with aggressive treatment of curative intent, increases with the patient’s age [6]. This may be a reflection of a higher perceived risk of toxicity and poor treatment tolerance due to the comorbidities (particularly cardiovascular disease) and poor performance status often encountered in the elderly.

Gemcitabine, an analog of cytosine arabinoside (ara-C), is a promising drug because of its single-agent activity and good tolerability in MBC when administered over a large dose range (800–1250 mg/m²) [19]. Response rates to gemcitabine therapy have ranged from 14% to 42%, median response duration from 5.6 months to 13.5 months, and TTP from 2.1 to 6.3 months, depending on the gemcitabine dose and schedule and the extent of prior treatment. Gemcitabine is also well tolerated in a variety of cancer patients, including the elderly [6]. In non-small-cell lung cancer (NSCLC), for example, patients aged >70 achieved a response rate of 25% [20].

On the basis of these findings, we conducted a randomized phase III trial to compare the efficacy of gemcitabine and epirubicin, both given as single agents, in postmenopausal women with MBC aged 60 or older. We also examined the quality of life (QoL), medical resource utilization, and toxicity of the two treatment arms.

**Patients and methods**

**Eligibility criteria**

Eligible patients were postmenopausal women aged 60 or older with histologic or cytologic diagnosis of clinically measurable metastatic (M1) breast cancer, as staged by the American Joint Committee on Cancer (AJCC), not amenable to endocrine therapy, surgery or radiation of curative intent. Clinically measurable disease was defined as bidimensionally measurable lesions, at least 1 cm in diameter, with clearly defined margins on X-ray, scans, or physical examination. Patients were not allowed to have prior anthracycline therapy, but could have received up to one prior nonanthracycline-based adjuvant therapy if the treatment was completed ≥1 year before study entry. Prior radiation therapy was allowed as long as the irradiated area was not the only source of measurable disease and the therapy was discontinued at least 3 weeks before enrollment. No prior chemotherapy for metastatic disease was allowed. Patients must have had a Karnofsky performance status (KPS) ≥60 and an estimated life expectancy of at least 12 weeks. Additional eligibility criteria were adequate bone-marrow reserve (white blood cell [WBC] ≥3.5 × 10⁹/l, platelets ≥100 × 10⁹/l, and hemoglobin ≥100 g/l), liver function (bilirubin ≤1.5 × the upper limit of normal [ULN] and alanine transaminase [ALT] and aspartate transaminase [AST] <5 × the ULN or ≤5 × the ULN in patients with known metastatic liver disease), and renal function (creatinine ≤1.5 × the ULN). Normal left ventricular ejection fraction (LVEF), as defined by scintigraphy or echocardiography, was also required. Patients who had active cardiac disease, severe psychiatric disease, central nervous system metastases, active infection, inflammatory breast cancer, or second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin) were excluded from the study.

Written informed consent was obtained from each patient prior to study entry. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki or the applicable guidelines on good clinical practice and was approved by the appropriate ethical review boards.

**Study design and sample size**

The primary end point of this multicenter, open-label, randomized, phase III trial was to compare the TTP in patients with MBC who were treated with gemcitabine monotherapy with that of patients treated with epirubicin monotherapy. Secondary end points were to compare the response rate, duration of response, survival time and QoL, and to evaluate the changes in medical resource utilization and toxicity of each treatment arm.

Patients were randomly assigned to gemcitabine or epirubicin. Patients were balanced with respect to the treatment in each stratum for each of the following prognostic factors using the Pocock and Simon algorithm [21]: KPS (60–70 or 80–100), prior adjuvant chemotherapy (yes or no), prior hormonal therapy for metastatic disease (yes or no), hepatic metastases at baseline (yes or no), and investigational center (one stratum for each center). The randomization probability factor was set at 1:0.

We planned to enroll a total of 440 patients (220 patients per treatment arm). This sample size should have allowed us to detect a difference of 9 weeks in median TTP between gemcitabine and epirubicin, assuming a median TTP of 26 weeks with epirubicin and 35 weeks with gemcitabine, with 80% power and a two-tailed significance level of 0.05.

**Treatment**

Patients received either gemcitabine 1200 mg/m² (intravenously over 30 min) on days 1, 8 and 15 or epirubicin 35 mg/m² (intravenously over 15 min) on days 1, 8 and 15 of a 28-day cycle. In the absence of progressive disease or intolerable toxicity, study treatment was to continue until a maximum of 12 cycles of gemcitabine or a maximum of eight cycles of epirubicin (cumulative dose of 840 mg/m²). The lifetime cumulative dose of epirubicin was not to exceed 900 mg/m² or 750 mg/m² for patients who had received radiotherapy to the mediastinal area. Patients received full supportive care, including growth factors for prolonged myelosuppression.

Dose modifications within a cycle for gemcitabine and epirubicin were based on weekly blood counts and assessment of nonhematologic toxicities. For an absolute granulocyte count (AGC) of < 1.0, WBC of 1.5–2.0, or platelet count of 50–75 × 10⁹/l, doses were reduced by 50%. Doses were omitted for an AGC of < 1.0, WBC < 1.5 or platelet count <50 × 10⁹/l. Treatment was reduced by 50% or omitted for World Health Organization (WHO) grade 3 toxicity (except nausea/vomiting and alopecia) and was omitted for grade 4 toxicity. Epirubicin was discontinued for evidence of clinical congestive heart failure or if LVEF fell on the radionuclide angiogram or echocardiography to <15% or to >45% if the total decrease was 10% or more from baseline (such as a decrease from 59% to 49%). If LVEF function returned, epirubicin could be restarted, with LVEF determinations performed before each cycle.

Doses for subsequent cycles were reduced by 50% of the starting dose of the previous cycle for sustained febrile neutropenia, grade 4 thrombocytopenia, or bleeding associated with thrombocytopenia. Escalation to the original dose was allowed for patients who tolerated the reduced doses. Doses were reduced by 25% for grade 3 non-hematologic toxicities (except nausea/vomiting and alopecia) and were reduced by 50% or omitted for grade 4 non-hematologic toxicities. Omitted or missed doses
were not given at a later time. Patients to whom the drug could not be administered for 6 weeks from the time of last treatment were discontinued. Study therapy was also discontinued for hypercalcemia requiring bisphosphonate therapy.

Baseline and treatment assessments

The disease status of each patient was assessed at baseline and throughout the study with the following tests: medical history and physical examination, evaluation of KPS, tumor measurement of palpable or visual lesions, chest X-ray, QoL questionnaires, and radiologic assessment of response (computed tomography [CT] scan, magnetic resonance imaging [MRI] or nuclear medicine scan). The same assessment method used to determine the disease status at baseline was used consistently for efficacy evaluation throughout the study.

All randomized patients were evaluated for the TTP and survival analyses on an intent-to-treat basis. All randomized patients who received at least three doses of gemcitabine or epirubicin were evaluated for tumor response. The objective response rate (complete response [CR] plus partial response [PR]) was assessed before every other cycle using standard WHO criteria. A panel of independent experts evaluated the response of each investigator-determined responder. Responses were confirmed no less than 4 weeks after the first observation. Time to progressive disease was measured from the time of randomization until the time of documented progressive disease, including death by any cause. Response duration was measured from the time the response was documented (CR) or the time of randomization (PR) until the date of the first observation of disease progression. Survival was defined as the time from randomization until death by any cause.

Figure 1. Flow of study participants.
All randomized patients with a baseline and at least one post-baseline assessment were included in the QoL analyses. Patients completed the EORTC QLQ-C30 (version 2.0) [22] and QLQ-BR23 (version 1.0) [23], the breast cancer-specific module, at baseline, at the start of each treatment cycle, and 4 weeks after the first dose of the last treatment cycle. Only patients for whom there were validated translations participated in the QoL portion of the study.

Medical resource utilization data were collected during the study to help estimate cost of treatment. These data, which were collected at each cycle, included location of chemotherapy administration (inpatient or outpatient), visits to health-care professionals, hospitalizations, medical procedures, blood transfusions, concomitant medications and post-study therapies.

All randomized patients who were treated with gemcitabine or epirubicin were evaluated for the safety analysis at the end of each cycle using WHO criteria. Additional safety assessments included number of units required for transfusions, full blood count and differential blood cell counts, blood chemistry tests, electrocardiogram (ECG), echocardiography or radionuclide angiogram for assessment of LVEF, and vital signs. Repeated LVEF determinations were performed in patients who reached a cumulative epirubicin dose of 630–840 mg/m².

Statistical methods

All interval estimates used a confidence level of 95%. Interval estimates for all rates were based on unadjusted normal approximations. Interval estimates for time-to-event quartiles were based on the method of Brookmeyer and Crowley [24]. All hypothesis tests comparing the two regimens used a significance level of \( \alpha = 0.0452 \). Comparisons of rates were performed using standard, unadjusted chi-square tests. Time-to-event comparisons were performed using the log-rank chi-square test [25]. The analyses of TTP, overall survival, time to tumor response, and duration of tumor response were performed using the following methods: Kaplan–Meier estimation (using the LIFETEST procedure in Statistical Application Software [SAS®]) of the distributions (by study therapy), including interval estimation of the quartiles, and overall log-rank (for late events) and Wilcoxon (for early events) chi-square tests [25] to compare distributions between study therapies. Quality-of-life data were analyzed as a comparison of changes from baseline between treatment arms, using analysis of variance (ANOVA) on rank-transformed data. Resource utilization data were summarized by treatment arm.

One interim analysis and one final analysis were performed. The interim analysis occurred at 50% enrollment, that is, when a total of 220 patients (110 per arm) were enrolled, under the auspices of an external data monitoring board (DMB). A significance level of 0.01 was used for the interim analysis. The final analysis was undertaken with a significance level of 0.0452, for an effective significance level of 5%.

Results

Patient characteristics

A total of 410 patients of the planned 440 patients were assessed for eligibility for the study between October 1996 and February 1999 (Figure 1). Study enrollment was halted in February 1999 at the time of the interim analysis because the primary end point was reached in favor of the control arm. Of the 410 patients assessed, 13 (seven gemcitabine and six epirubicin) were ineligible due to insufficient therapy, prior chemotherapy, unconfirmed diagnosis and no bidimensionally measurable lesions, leaving 397 patients randomized at 68 sites in 17 countries. This manuscript presents the final results for all 397 patients.

Tables 1 and 2 present summaries of patient and disease characteristics and prior treatments, respectively. Approximately 81% of the patients were Caucasians. The median KPS was 90 (range 60–100). Most patients (78%) had ductal breast carcinoma. Approximately 20% of patients had received prior adjuvant chemotherapy. Generally, baseline patient and disease characteristics and prior antineoplastic treatments were well balanced between the two treatment arms. A higher proportion of gemcitabine patients than epirubicin patients had ≥4 sites of disease (22.2% versus 16.6%, respectively); however, the difference was not statistically significant (\( P = 0.165 \)). More patients on the gemcitabine arm had lung and bone metastases than did those on the epirubicin arm (a difference between treatment arms of approximately 10%).

Treatment administration

A total of 699 complete cycles of gemcitabine was administered to 185 patients, for a mean cycle number of 3.5 (range 0–12); five patients randomized to gemcitabine did not receive a full cycle of therapy. A total of 192 patients received 917 cycles of epirubicin, for a mean cycle number of 4.6 (range 0–10).

The median delivered doses were 1100 mg/m² (range 343–1266 mg/m²) for gemcitabine and 34 mg/m² (range 12–39 mg/m²) for epirubicin. Gemcitabine doses were reduced (7% of doses) or omitted (9% of doses) primarily due to myelosuppression, yielding a relative dose intensity of 86.9% when taking into account 100 delays in that arm. Epirubicin doses were reduced (5% of doses) or omitted (5% of doses) primarily due to symptomatic events (such as stomatitis), yielding a relative dose intensity of 90.6% when taking into account 169 delays in that arm. Epirubicin-treated patients had more delays due to leukopenia.

Efficacy

All 397 randomized patients qualified for the analyses of TTP and overall survival. A total of 369 patients (183 gemcitabine and 186 epirubicin) qualified for the response analysis. The 15 patients who were randomized but did not receive treatment were excluded from this analysis, in addition to the 13 ineligible patients.

Tables 3 and 4 present a summary of results for time-to-event end points and independently assessed tumor response, respectively. Epirubicin demonstrated statistically significant superiority to gemcitabine in TTP (6.1 and 3.4 months, respectively; HR = 1.678 [95% CI 1.344–2.095]; \( P = 0.0001 \)) (Figure 2), overall survival (19.1 and 11.8 months, respectively; \( P = 0.0004 \)), and peer-reviewed response rate (40.3% and 16.4%, respectively; \( P < 0.0001 \)). Because the study was stopped early, when the primary end point was reached in favor of the control arm, all post-study follow-up ceased at this time. Hence, censoring was high, in particular for survival (more than 50% in both arms). Investigator-assessed response
rates for epirubicin and gemcitabine were 42.5% and 17.5%, respectively. Liver and lung were the most common sites of progressive disease. There were no statistically significant differences between the epirubicin and gemcitabine treatment arms for duration of response (9.9 and 7.8 months, respectively).

A total of 248 patients (120 gemcitabine and 128 epirubicin) were included in the QoL analysis. The number of observations decreased rapidly over time, and neither of the treatment arms offered a clear overall advantage in QoL. There were no significant differences between arms at baseline. Between-arm differences in change from baseline were noted in six of the 23 QoL scales. Gemcitabine-treated patients reported greater deterioration of physical functioning, while epirubicin-treated patients reported greater increases in nausea/vomiting, greater deterioration of body image, and greater incidence and/or severity of side-effects. However, epirubicin-treated patients also reported greater pain and arm-symptom relief. Mean changes from baseline for these scales are shown in Figure 3.

Medical resource utilization, which was summarized for all 397 randomized patients, differed slightly between the treatment arms. The number of hospital admissions was similar between arms (389 for gemcitabine versus 378 for epirubicin), with drug administration accounting for two-thirds of these admissions. The number of health-care professional visits was slightly higher in the gemcitabine arm (257 versus 219). A variety of medical procedures were reported, with chest X-rays being the most common in both treatment arms. Use of granulocyte colony-stimulating factors was low in both treatment arms (3.0% for gemcitabine versus 4.5% for epirubicin), as was erythropoietin (1.5% versus 0). Similar numbers of patients received parenteral antibiotics (13.1% for gemcitabine versus 13.6% for epirubicin). More patients in the epirubicin arm received 5-HT3 antagonists (81.9% versus 60.6%), anti-fungals (15.1% versus 6.6%), and antivirals (3.0% versus 0). The use of transfusions is discussed below.

Table 1. Summary of baseline patient and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine (n = 198)</th>
<th>Epirubicin (n = 199)</th>
<th>Total (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>69 (59–91)</td>
<td>68 (60–85)</td>
<td>68 (59–91)</td>
</tr>
<tr>
<td>KPS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>16 (8.1)</td>
<td>10 (5.1)</td>
<td>26 (6.6)</td>
</tr>
<tr>
<td>70</td>
<td>23 (11.7)</td>
<td>31 (15.7)</td>
<td>54 (13.7)</td>
</tr>
<tr>
<td>80</td>
<td>51 (25.9)</td>
<td>44 (22.2)</td>
<td>95 (24.1)</td>
</tr>
<tr>
<td>90</td>
<td>69 (35.0)</td>
<td>69 (34.8)</td>
<td>138 (34.9)</td>
</tr>
<tr>
<td>100</td>
<td>35 (17.8)</td>
<td>40 (20.2)</td>
<td>75 (19.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2.0)</td>
<td>5 (2.5)</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Differentiation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>9 (4.6)</td>
<td>7 (3.5)</td>
<td>16 (4.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>55 (27.9)</td>
<td>65 (32.8)</td>
<td>120 (30.4)</td>
</tr>
<tr>
<td>Poor</td>
<td>43 (21.8)</td>
<td>50 (25.3)</td>
<td>93 (23.5)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>6 (3.0)</td>
<td>5 (2.5)</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Unknown/unspecified</td>
<td>85 (42.9)</td>
<td>72 (36.2)</td>
<td>157 (39.5)</td>
</tr>
<tr>
<td>ER status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>67 (33.8)</td>
<td>71 (35.7)</td>
<td>138 (34.8)</td>
</tr>
<tr>
<td>Negative</td>
<td>41 (20.7)</td>
<td>39 (19.6)</td>
<td>80 (20.2)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Unknown/not done</td>
<td>88 (44.4)</td>
<td>86 (43.2)</td>
<td>174 (43.8)</td>
</tr>
<tr>
<td>Number of metastatic sites, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>41 (20.7)</td>
<td>47 (23.6)</td>
<td>88 (22.2)</td>
</tr>
<tr>
<td>2–3</td>
<td>113 (57.1)</td>
<td>119 (59.8)</td>
<td>232 (58.4)</td>
</tr>
<tr>
<td>≥4</td>
<td>44 (22.2)</td>
<td>33 (16.6)</td>
<td>77 (19.4)</td>
</tr>
<tr>
<td>Sites of disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>95 (48.0)</td>
<td>77 (38.7)</td>
<td>172 (43.3)</td>
</tr>
<tr>
<td>Liver</td>
<td>68 (34.3)</td>
<td>70 (35.2)</td>
<td>138 (34.8)</td>
</tr>
<tr>
<td>Non-visceral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>87 (43.9)</td>
<td>66 (33.2)</td>
<td>153 (38.5)</td>
</tr>
<tr>
<td>Lymph node, NOS</td>
<td>68 (34.3)</td>
<td>65 (32.7)</td>
<td>133 (33.5)</td>
</tr>
<tr>
<td>Otherb</td>
<td>85 (42.9)</td>
<td>103 (51.8)</td>
<td>188 (47.4)</td>
</tr>
</tbody>
</table>

aOne patient who was 59 years old was enrolled and treated in error.
bOther included breast, skin, NOS and pleura.

differences between the epirubicin and gemcitabine treatment arms for duration of response (9.9 and 7.8 months, respectively).

A total of 248 patients (120 gemcitabine and 128 epirubicin) were included in the QoL analysis. The number of observations decreased rapidly over time, and neither of the treatment arms offered a clear overall advantage in QoL. There were no significant differences between arms at baseline. Between-arm differences in change from baseline were noted in six of the 23 QoL scales. Gemcitabine-treated patients reported greater deterioration of physical functioning, while epirubicin-treated patients reported greater increases in nausea/vomiting, greater deterioration of body image, and greater incidence and/or severity of side-effects. However, epirubicin-treated patients also reported greater pain and arm-symptom relief. Mean changes from baseline for these scales are shown in Figure 3.

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Toxicity

A total of 382 (190 gemcitabine-treated and 192 epirubicin-treated) patients were assessed for toxicity. Overall, both gemcitabine and epirubicin were well tolerated in this elderly patient population (Table 5). For both gemcitabine and epirubicin, WHO grade 3/4 laboratory toxicities were primarily hematologic, with the most common toxicities being neutropenia (25.3% and 17.9%, respectively) and leukopenia (14.3% and 19.3%, respectively). However, hematologic toxicities were not commonly associated with clinical events such as transfusions (15.2% and 11.1% of patients, respectively, had

Table 2. Summary of prior therapy

<table>
<thead>
<tr>
<th>Prior therapy, n (%)</th>
<th>Gemcitabine (n = 198)</th>
<th>Epirubicin (n = 199)</th>
<th>Total (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>191 (96.5)</td>
<td>191 (96.0)</td>
<td>382 (96.2)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>103 (52.0)</td>
<td>97 (48.7)</td>
<td>200 (50.4)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>39 (19.7)</td>
<td>39 (19.6)</td>
<td>78 (19.6)</td>
</tr>
<tr>
<td>Adjuvantb</td>
<td>39 (19.7)</td>
<td>34 (17.1)</td>
<td>73 (18.4)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>0</td>
<td>4 (2.0)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Metastaticb</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>2 (1.0)</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>134 (67.7)</td>
<td>131 (65.8)</td>
<td>265 (66.8)</td>
</tr>
<tr>
<td>Not specified</td>
<td>9 (4.5)</td>
<td>5 (2.5)</td>
<td>14 (3.5)</td>
</tr>
</tbody>
</table>

aThree patients (two on the gemcitabine arm and one on the epirubicin arm) who received two lines of prior adjuvant chemotherapy were enrolled and treated in error.
bOne patient who received prior chemotherapy in the metastatic setting was enrolled and treated in error.

patients reported greater deterioration of physical functioning, while epirubicin-treated patients reported greater increases in nausea/vomiting, greater deterioration of body image, and greater incidence and/or severity of side-effects. However, epirubicin-treated patients also reported greater pain and arm-symptom relief. Mean changes from baseline for these scales are shown in Figure 3.
at least one transfusion), grade 3/4 infection (2.1% and 3.6%, respectively), or grade 3/4 hemorrhage (0.5% and 0%, respectively). Among the four gemcitabine-treated patients with grade 4 thrombocytopenia, only two required platelet transfusions. Twenty-seven gemcitabine-treated patients and 22 epirubicin-treated patients received red blood cell transfusions. Elevated liver enzymes were noted in 5.5% and 2.6% of gemcitabine-treated and epirubicin-treated patients, respectively; however, they were not clinically significant.

Although WHO grade 3/4 non-laboratory toxicities were generally infrequent in both the gemcitabine and epirubicin arms, alopecia (1.1% and 55.2%, respectively) and mucositis (0% and 7.8%, respectively) were more common with epirubicin, and diarrhea (2.1% and 0.5%, respectively) was more common with gemcitabine. Of the 89 epirubicin-treated patients with post-baseline LVEF measurements, four patients had absolute LVEF values less than 45%, and 24 patients had at least a 10% decline in LVEF values from baseline. In addition, 47 (23.6%) epirubicin-treated patients and 34 (17.2%) gemcitabine-treated patients had cardiac events of clinical concern. Of note, 10 patients discontinued epirubicin treatment due to cardiac events, while only one patient discontinued gemcitabine treatment due to a cardiac event.

When viewing toxicities by age (<70 versus ≥70 years), minor differences in some toxicities were noted. Grade 4 leukopenia was more common in the older patients on the epirubicin arm, but this increase was not seen in the incidence of grade 4 neutropenia. In addition, mucositis occurred more frequently in epirubicin-treated patients >_70 years of age. On the gemcitabine arm, pulmonary toxicity was slightly more frequent in patients >_70 years of age.

While serious adverse events related to study therapy were reported more frequently in the gemcitabine arm than in the epirubicin arm (20.7% and 13.6%, respectively; P = 0.063), clinically significant related adverse events leading to study therapy discontinuation occurred more commonly in the epirubicin treatment arm than in the gemcitabine arm (8.5% and 6.1%, respectively; P = 0.441). Of the 28 deaths occurring on study (17 deaths in the gemcitabine arm, 11 deaths in the epirubicin arm), three deaths were considered possibly or probably related to study therapy (gemcitabine in all three cases), while 13 (46%) were considered related to study disease. The three related deaths were due to myocardial infarction (possibly related), cellulitis (possibly related) and hemorrhage (probably related), and occurred in patients ≥70 years of age.

**Discussion**

In this multicenter, open-label, randomized, phase III study in postmenopausal women with MBC aged 60 or older, both gemcitabine and epirubicin monotherapy were active treatments, although the latter was more active. Epirubicin was significantly superior to gemcitabine in TTP, overall survival and independently assessed response rate, whereas response duration was similar in both treatment arms. Neither treatment arm showed any clear advantage in QoL or medical resource utilization. Key patient and disease characteristics, as well as prior treatment histories, were generally well balanced between study arms. The relatively minor imbalances of soft tissue disease and lower tumor burden in the epirubicin arm of
our study are unlikely to account for the lower than anticipated efficacy results observed in the gemcitabine arm.

To our knowledge, the current trial is the only phase III study evaluating gemcitabine and epirubicin as first-line monotherapy in postmenopausal (>60 years) patients with MBC. Historical data are limited to a few phase II studies that evaluated smaller patient populations. In several phase II studies that applied similar weekly regimens as those used in the current study, gemcitabine produced TTP ranging from 2.1 to 5.1 months and response rates from 14% to 37% in mostly chemo naive patients [19]. In a phase II study conducted in 46 postmenopausal women, of whom about 90% were chemo naive, low-dose epirubicin produced a response rate of 43% in 42 evaluable patients [16]. Two phase III studies, one comparing epirubicin versus epirubicin plus cisplatin [26] and one comparing doxorubicin versus paclitaxel [27], also demonstrated the effectiveness of anthracyclines as first-line therapy.

Treatment in both study arms was generally well tolerated in this older, postmenopausal population, as indicated by the low percentages of dose adjustments required and by the few grade 3/4 toxicities and minimal clinical sequelae noted. In addition, there were no clinically relevant differences observed based on age (<70 versus ≥70 years) within each treatment, and both treatments were well tolerated regardless of age. This study did not demonstrate any new or unanticipated toxicities for either gemcitabine or epirubicin therapy. For both gemcitabine and epirubicin, the main grade 3/4 laboratory toxicities were primarily hematologic, of which the most common toxicity was neutropenia (25.3% and 17.9%, respectively). Although liver metastases were common in both arms and were a common site of progression, elevated liver enzyme rates for both drugs were low, and no patients discontinued or died due to liver toxicity. Of the 28 deaths that occurred in this study, 13 (46%) were related to breast cancer. The other deaths might have been attributed to the age of the patients or to concurrent diseases, and three deaths were considered related to study therapy (gemcitabine).

Epirubicin treatment of postmenopausal women tends to result in more pronounced toxicity, including nausea, vomiting and alopecia, compared with that in premenopausal women [28, 29]. More importantly, epirubicin is associated with myocardial toxicity, including potentially fatal congestive heart failure (CHF). In the current study, epirubicin was generally well tolerated, although approximately 31% of patients demonstrated radiologic evidence of cardiac dysfunction during or after therapy. Both treatments resulted in similar incidences of cardiac events of clinical concern (17.2% gemcitabine and 23.6% epirubicin); however, 10 epirubicin-treated

![Figure 3. Mean changes from baseline in physical functioning, nausea/vomiting, pain (top, left to right), body image, arm symptoms, and systemic therapy side-effects (bottom, left to right). Positive changes indicate improvement for physical functioning and body image, and worsening for nausea/vomiting, pain, arm symptoms, and systemic therapy side-effects. Scores on all scales range from 0 to 100.](image-url)
patients discontinued due to cardiac events compared with only one gemcitabine-treated patient. Epirubicin produced more grade 3/4 alopecia (55.2% compared with 1.1%) and mucositis (7.8% compared with 0%). Of note, oral symptoms, namely stomatitis, necessitated epirubicin-dose reductions and omissions. Overall, adverse events leading to study therapy discontinuation occurred more frequently in the epirubicin arm (8.5% compared with 6.1%).

The efficacy and safety profile of gemcitabine supports its investigation as a combination agent for the treatment of MBC. The combination of gemcitabine and epirubicin has been shown to be active and tolerable in patients with MBC [30–34]. The combination of gemcitabine and paclitaxel has also demonstrated activity in chemonaive patients and those considered refractory to anthracycline treatment [35–39]. In these phase II studies, TTP ranged from 7 to 7.5 months and response rates from 42% to 68% for the combination. Recently, studies of gemcitabine combinations in the treatment of breast cancer have been using a 21-day schedule to avoid the toxicity and subsequent dose reductions or omissions often associated with the day-15 dose. In a recent interim analysis of a phase III trial, a 21-day regimen of gemcitabine plus paclitaxel administered to anthracycline-pretreated patients was found to be statistically superior to paclitaxel monotherapy in TTP, progression-free survival and response, while demonstrating a trend toward superiority for overall survival and a toxicity profile consistent with that of gemcitabine and paclitaxel as single agents [40]. Thus, the addition of gemcitabine may improve the efficacy of paclitaxel treatment in patients with advanced breast cancer.

Although this study may not be considered highly relevant to the care of patients presenting with MBC who have received prior anthracycline in the adjuvant setting, it does provide important information on the tolerability of chemotherapy in elderly patients with MBC.

In conclusion, the results of the current trial, which is the first randomized study of chemotherapy in older postmenopausal women with MBC, have demonstrated good tolerance in patients with MBC [30–34]. The combination of gemcitabine and epirubicin has been shown to be active and tolerable in patients with MBC [30–34]. The combination of gemcitabine and paclitaxel has also demonstrated activity in chemonaive patients and those considered refractory to anthracycline treatment [35–39]. In these phase II studies, TTP ranged from 7 to 7.5 months and response rates from 42% to 68% for the combination. Recently, studies of gemcitabine combinations in the treatment of breast cancer have been using a 21-day schedule to avoid the toxicity and subsequent dose reductions or omissions often associated with the day-15 dose. In a recent interim analysis of a phase III trial, a 21-day regimen of gemcitabine plus paclitaxel administered to anthracycline-pretreated patients was found to be statistically superior to paclitaxel monotherapy in TTP, progression-free survival and response, while demonstrating a trend toward superiority for overall survival and a toxicity profile consistent with that of gemcitabine and paclitaxel as single agents [40]. Thus, the addition of gemcitabine may improve the efficacy of paclitaxel treatment in patients with advanced breast cancer.

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In conclusion, the results of the current trial, which is the first randomized study of chemotherapy in older postmenopausal women with MBC, have demonstrated good tolerance of single-agent epirubicin and gemcitabine in this population. However, epirubicin was more active than gemcitabine. These results confirm that anthracyclines—represented in this trial by epirubicin—remain important drugs as first-line treatment of MBC. The current evidence also suggests that further development of single-agent gemcitabine in MBC should focus on patients who have received prior anthracycline or on developing active gemcitabine-based combinations.

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