



Michele Sassi. La Digue Island, c. 2001. Seychelles Islands, Indian Ocean. Photograph.

*Regimens containing higher doses of epirubicin prolong relapse-free and overall survival rates compared with standard therapies.*

# The Expanding Role of Epirubicin in the Treatment of Breast Cancer

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**A**djuvant treatment of early breast cancer has experienced major changes in the last 25 years. Since the mid 1970s, when cyclophosphamide, methotrexate and fluorouracil (CMF) resulted in statistically significant and clinically meaningful improvements in disease-free and overall survival, the use of adjuvant chemotherapy has become common practice worldwide. Anthracyclines are considered to be among the most active available agents to treat breast cancer and have become core components of adjuvant regimens. Anthracycline-containing polychemotherapy regimens provide a significant benefit over CMF.

Regimens containing epirubicin are generally associated with prolongation in relapse-free and overall survival rates compared with standard therapies including CMF. Epirubicin-taxane combinations are active in treating metastatic breast cancer and do not appear to be associated with any pharmacokinetic interactions. Ongoing research is focusing on combining anthracyclines with taxanes in an effort to continue to improve outcomes following adjuvant therapy.

## Introduction

Breast cancer accounts for 31% of all cancers diagnosed and 15% of deaths due to cancer in women in the United States.<sup>1</sup> By eradicating systemic micrometastases, systemic adjuvant treatment improves the outcome of women with early-stage breast cancer who appear free of disease after local treatment. Drugs used in the adjuvant setting are those that demonstrate high antitumor activity in women with metastatic breast cancer.

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Adjuvant chemotherapy for early breast cancer has experienced major changes in the past 25 years. The combination of cyclophosphamide, methotrexate, and fluorouracil (CMF)<sup>2,3</sup> has been considered the “gold standard” for treating early-stage breast cancer in the adjuvant setting since the middle 1970s. As adjuvant therapies evolved, anthracyclines, particularly doxorubicin, became a core component of these regimens; however, doxorubicin is associated with numerous toxicities including cardiotoxicity, nausea and vomiting, and myelosuppression. Epirubicin, an anthracycline with less toxicity at equimolar doses, represents an alternative to doxorubicin for treating breast cancer. It has been extensively studied in the treatment of breast cancer and is highly active in both the adjuvant and metastatic treatment settings.

Results of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) worldwide overview analysis of polychemotherapy for early breast cancer demonstrated a small but significant benefit in relapse-free and overall survival with anthracycline-containing regimens compared with CMF.<sup>2</sup> These findings, coupled with results of large phase III trials, led to the recent statement from the National Institutes of Health (NIH) Consensus Development Conference on Adjuvant Therapy

for Breast Cancer recommending adjuvant polychemotherapy, particularly anthracycline-containing, for most women with primary breast cancers larger than 1 cm in diameter, regardless of nodal, menopausal, or hormone receptor status.<sup>4</sup> The use of anthracycline-containing adjuvant chemotherapy regimens is universally accepted; however, optimal drugs and drug combinations, doses, and schedules remain to be defined.

## Anthracycline-Based Chemotherapy in Metastatic Breast Cancer

The evolution of adjuvant therapies is typically protracted. New agents and new combinations are first evaluated in the metastatic setting, and those that show activity are then evaluated as adjuvant therapy. Anthracyclines have long been considered to be among the most active single agents available for the treatment of breast cancer and play a major role in both metastatic disease and as adjuvant therapy. Doxorubicin, which has been used extensively in the treatment of metastatic breast cancer and is a standard component of many combination chemotherapy regimens, is limited by potential cardiotoxicity with cumulative doses of 450 mg/m<sup>2</sup> or higher.

Table 1. — Comparison of Equimolar Doses of Epirubicin and Doxorubicin in Metastatic Breast Cancer: Summary of Clinical Trials

| Study   | No. of Patients | Regimen* | Response Rate (%) | Median Survival (mo) | No. of Patients With CHF/Other Cardiac Events | Percent of Patients With Grade 3/4 Nausea/Vomiting | Percent of Patients With Grade 3/4 Neutropenia |
|---|-----------------|----------|-------------------|----------------------|---|--|--|
| French Epirubicin Study Group <sup>5</sup>    | 113             | FAC-50   | 52                | 17                   | 3 / 5   | 13 <sup>†</sup>                                    | 5 <sup>†</sup>                                 |
|   | 117             | FEC-50   | 50                | 15                   | 0 / 0   | 8  | 2  |
| Italian Multicenter Breast Study <sup>6</sup> | 221             | FAC-50   | 56                | 20                   | 4 / 21  | 47   | 28   |
|   | 222             | FEC-50   | 54                | 19                   | 1 / 8   | 35   | 15   |
| Lopez et al <sup>7</sup>                      | 46              | FAC-50   | 46                | 16                   | 3 / 0   | 72   | 24   |
|   | 48              | FEC-50   | 44                | 14                   | 0 / 1   | 51   | 15   |
| Heidemann et al <sup>8</sup>                  | 51              | AC-40    | 42                | NR                   | 0 / 4   | NR   | NR   |
|   | 66              | EC-40    | 42                | NR                   | 1 / 3   | NR   | NR   |
| Lawton et al <sup>9</sup>                     | 28              | A-70     | 36                | 8                    | 0 / 1   | 22   | 7 <sup>†</sup>                                 |
|   | 28              | E-70     | 32                | 10                   | 1 / 0   | 18   | 3  |
| Gasparini et al <sup>10</sup>                 | 21              | A-20     | 38                | 11                   | 1 / 3   | 5  | 5  |
|   | 22              | E-20     | 36                | 12                   | 0 / 2   | 0  | 0  |
| Castiglione et al <sup>11</sup>               | 50              | A-20     | 29                | 15                   | NR  | NR   | NR   |
|   | 50              | E-20     | 20                | 13                   | NR  | NR   | NR   |

\* Numbers represent doxorubicin or epirubicin dose in mg/m<sup>2</sup>.

<sup>†</sup> Data reported as percentage of treatment courses rather than patients.

A = doxorubicin

F = fluorouracil

C = cyclophosphamide

CHF = congestive heart failure

E = epirubicin

NR = not reported

Epirubicin, the 4'-epimer of doxorubicin, is also highly active in the treatment of metastatic breast cancer. At equimolar doses, epirubicin-based regimens have been shown to be equally efficacious and less toxic than doxorubicin-based regimens in clinical trials of metastatic breast cancer (Table 1).<sup>5-11</sup> No significant differences in response rate or median survival time were observed, and overall, patients receiving epirubicin-based therapy experienced less congestive heart failure, nausea and vomiting, and neutropenia compared with those receiving doxorubicin-based therapy.

## Anthracycline-Based Adjuvant Therapy for Breast Cancer

CMF became the "gold standard" adjuvant regimen based on studies reported in the early 1970s by investigators at the Istituto Nazionale Tumori in Milan, Italy. Bonadonna and colleagues<sup>3</sup> demonstrated that disease-free and overall survival rates significantly improved

with CMF as adjuvant chemotherapy following mastectomy. In the 1990s, anthracycline-based adjuvant regimens gained in popularity due to results of large phase III trials and to findings from the EBCTCG overview analysis<sup>2</sup> of polychemotherapy for early breast cancer, which compared anthracycline-containing regimens with CMF as adjuvant therapy. The EBCTCG overview analysis demonstrated that, compared with standard CMF alone, anthracycline-containing regimens reduced the annual risk of breast cancer recurrence by 12% ( $P=.006$ ) and the annual risk of death by 11% ( $P=.02$ ), equating to a 3.2% absolute reduction in recurrence and a 2.7% absolute reduction in mortality at 5 years.<sup>2</sup>

Consensus statements from US and international panels and US network practice guidelines recommend the use of anthracycline-containing regimens as adjuvant therapies of most women with early breast cancer, specifically node-positive disease in one set of guidelines.<sup>4,12,13</sup> The International Consensus Statement<sup>12</sup> was recently updated at the 2001 St Gallen Interna-

Table 2. — Doxorubicin-Based Regimens vs CMF as Adjuvant Therapy for Early Breast Cancer: Summary of Phase III Trials

|                             | Study   | No. of Patients     | Treatment                               | Disease-Free Survival, % | Overall Survival, %         |                       |                       |
|-----------------------------|---|---------------------|---|--------------------------|-----------------------------|-----------------------|-----------------------|
| Node-Positive Breast Cancer | NSABP B-15 <sup>14</sup>                      | 2,194               | AC × 4                                  | 62 (3 y)                 | 83 (3 y)                    |                       |                       |
|                             |   |                     | CMF × 6                                 | 63                       | 82                          |                       |                       |
|                             |   |                     | AC × 4 → 6-mo rest → CMF × 3            | 68                       | NR                          |                       |                       |
|                             | Oncofrance <sup>15</sup>                      | 248                 | AVCF × 12<br>CMF × 12                   | 53* (16 y)<br>36         | 56* (16 y)<br>41            |                       |                       |
|                             | Southeastern Cancer Study Group <sup>16</sup> | 528                 | CAF × 6<br>CMF × 6                      | NR<br>NR                 | 74 (5 y)<br>68              |                       |                       |
| Node-Negative Breast Cancer | US Intergroup <sup>17</sup>                   | 531                 | FAC-M × 4                               | 50 (5 y)                 | 61 (5 y)                    |                       |                       |
|                             |   |                     | CMFVP × 1 y                             | 55                       | 64                          |                       |                       |
|                             |   |                     | Istituto Nazionale Tumori <sup>18</sup> | 486                      | CMF × 8 → A × 4<br>CMF × 12 | 72 (5 y)<br>74        | 86 (5 y)<br>89        |
|                             |   |                     | US Intergroup <sup>19</sup>             | 2,691 <sup>†</sup>       | CAF × 6                     | 85 <sup>‡</sup> (5 y) | 92 <sup>‡</sup> (5 y) |
|                             | CMF × 6                                       | 82                  |   |                          | 90                          |                       |                       |
| CAF × 6 + tamoxifen         | 87  | 93                  |   |                          |                             |                       |                       |
| CMF × 6 + tamoxifen         | 85  | 91                  |   |                          |                             |                       |                       |
| NSABP B-23 <sup>20</sup>    | 1,982   | AC × 4              | 87 (5 y)                                | 90 (5 y)                 |                             |                       |                       |
|                             |   | AC × 4 + tamoxifen  | 87                                      | 90                       |                             |                       |                       |
|                             |   | CMF × 6             | 88                                      | 89                       |                             |                       |                       |
|                             |   | CMF × 6 + tamoxifen | 87                                      | 89                       |                             |                       |                       |

\*  $P \leq .01$ .

<sup>†</sup> Patients were high risk and randomized to CAF or CMF ± tamoxifen.

<sup>‡</sup>  $P < .05$ .

A = doxorubicin

P = prednisone

C = cyclophosphamide

V = vincristine

F = fluorouracil

NR = not reported

M = methotrexate

NSABP = National Surgical Adjuvant Breast and Bowel Project

tional Conference on Adjuvant Therapy of Primary Breast Cancer. During the consensus meeting, the panel agreed that there are patients who respond to CMF; however, anthracycline-based chemotherapy is the preferred choice of treatment.

### *Doxorubicin-Based Regimens vs CMF*

To date, a doxorubicin-containing regimen has proved itself superior to standard CMF only as adjuvant treatment of early-stage breast cancer in two randomized trials — one in patients with node-positive disease and one in node-negative disease (Table 2).<sup>14,20</sup> An Oncofrance trial compared 12 cycles of doxorubicin (30 mg/m<sup>2</sup>), vincristine, cyclophosphamide, and fluorouracil (AVCF) with CMF in 249 patients with node-positive breast cancer and demonstrated improved overall and disease-free survival with AVCF compared with CMF.<sup>15</sup> Although the doxorubicin-based AVCF regimen prolonged survival, a 12-month treatment regimen is impractical and not considered standard adjuvant therapy.

A study performed by the US Intergroup compared cyclophosphamide, doxorubicin, fluorouracil (CAF) with CMF in 2,691 patients with high-risk node-negative breast cancer.<sup>19</sup> Both treatment groups included patients treated with or without tamoxifen. Results demonstrated a small but statistically significant superiority in 5-year disease-free survival rate and overall survival rate for patients receiving CAF compared with CMF. However, CAF produced more granulocytopenia, nausea, vomiting, stomatitis, and alopecia than did CMF.

Two other large randomized trials, one conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP)<sup>14</sup> and the other by the Southeastern Cancer Study Group (SECSG),<sup>16</sup> failed to demonstrate a significant improvement in survival between patients treated with a doxorubicin-containing regimen and those treated with standard CMF. Interestingly, the NSABP trial<sup>14</sup> was instrumental in establishing AC as standard adjuvant treatment for node-positive breast cancer in the United States. Although AC was not

proven to be superior to CMF, a regimen of 4 cycles of AC was shown to be less toxic and less costly than 6 cycles of CMF.

### *Epirubicin-Based Regimens vs CMF*

The equivalent efficacy and improved toxicity profile associated with epirubicin compared with doxorubicin in the metastatic setting prompted its investigation as adjuvant treatment for early-stage breast cancer. Five reported trials have compared an epirubicin-containing adjuvant regimen with CMF as adjuvant therapy of women with early breast cancer.<sup>21-25</sup>

The International Collaborative Cancer Group (ICCG) conducted a randomized trial comparing two alternative schedules of CMF — CMF1 (oral) and CMF2 (intravenous) — and fluorouracil, epirubicin (50 mg/m<sup>2</sup>), and cyclophosphamide (FEC1 and FEC2) in 759 premenopausal women with axillary node-positive breast cancer.<sup>21</sup> At a median follow-up time of 4.5 years, the relapse-free and overall survival rates between CMF1 and FEC1 did not differ; however, improved relapse-free rates ( $P=.03$ ) and overall survival rates (86.6% vs 73.8%,  $P=.02$ ) were observed in patients receiving FEC2 (fluorouracil and cyclophosphamide 600 mg/m<sup>2</sup> each on days 1 and 8, epirubicin 50 mg/m<sup>2</sup> on day 1 q 4 weeks × 6) compared with CMF2 (fluorouracil and cyclophosphamide 600 mg/m<sup>2</sup> each on days 1 and 8, methotrexate 40 mg/m<sup>2</sup> on days 1 and 8 q 4 weeks × 6).

The MA-5 trial<sup>22</sup> conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) compared a dose intensive combination of cyclophosphamide, epirubicin, and fluorouracil (CEF) with CMF (at the original doses and administration schedule) in 710 premenopausal and perimenopausal women with node-positive breast cancer. Patients in the CEF group received lower doses of cyclophosphamide and fluorouracil than those in the CMF group in order to improve tolerability of the dose-intensive epirubicin treatment. The epirubicin dose was 120 mg/m<sup>2</sup> every 28 days (ie, administered in 2 equal doses on day 1 and

Table 3. — Results of the National Cancer Institute of Canada MA-5 Trial of CEF vs CMF<sup>22</sup>

|  | 5-Year Relapse-Free Survival, %      |                   |         | 5-Year Overall Survival, % |                |         |
|--|--------------------------------------|-------------------|---------|----------------------------|----------------|---------|
|  | CEF<br>(n=351)                       | CMF<br>(n=359)    | P Value | CEF<br>(n=351)             | CMF<br>(n=359) | P Value |
| All patients                           | 63                                   | 53                | .009    | 77                         | 70             | .03     |
| 1-3 positive nodes                     | 69                                   | 62                | NR      | 82                         | 78             | NR      |
| >3 positive nodes                      | 53                                   | 39                | NR      | 70                         | 58             | NR      |
| C = cyclophosphamide<br>E = epirubicin | F = fluorouracil<br>M = methotrexate | NR = not reported |         |                            |                |         |

day 8 of each cycle), which corresponds to twice the dose of doxorubicin used in standard CAF regimens. Because the incidence of cardiotoxicity is less with equimolar doses of epirubicin compared with doxorubicin, increasing the dose intensity of this agent is a reasonable approach. At a median follow-up time of 5 years, the relapse-free and overall survival rates were significantly longer for patients receiving CEF compared with CMF despite lower doses of cyclophosphamide and fluorouracil and lower mean relative received dose intensity (.77 vs .88, Table 3). Treatment with CEF was associated with a 29% reduction in the risk of relapse and a 19% reduction in the risk of death. Of note, this study was not designed to have the statistical power to detect outcome differences in the subgroups of patients with lymph node-positive disease; however, trends in survival favored the use of CEF in patients with 1-3 and >3 positive lymph nodes. With longer follow-up, these differences may become statistically significant. Grade 3 or 4 neutropenia occurred in both treatment groups, with febrile neutropenia that required hospitalization occurring more frequently in the CEF group compared with the CMF group (8.5% vs 1.1%,  $P=.0001$ ). With respect to late toxicities, congestive heart failure was reported in 4 CEF-treated patients (1.1%) and in 1 CMF-treated patient (0.3%), while acute leukemia occurred in 5 CEF-treated patients (4 = myeloid, 1 = lymphoid) and in 1 CMF-treated patient.

The Danish Breast Cancer Cooperative Group (DBCG)<sup>23</sup> reported results of a study designed to determine if the therapeutic gains observed with anthracycline-based therapy in the metastatic setting would translate into the adjuvant setting in three subgroups of patients. Group A included premenopausal women with node-negative disease and a grade 2-3 tumor, group B included premenopausal women with node-positive, receptor-negative or -unknown tumor, and

group C included postmenopausal women with node-positive, receptor-negative or -unknown tumors. Following primary local therapy patients were randomized to receive treatment with CMF, CEF (epirubicin 60 mg/m<sup>2</sup>), CMF plus pamidronate, or CEF plus pamidronate. Regimens were repeated every 3 weeks for 9 cycles. A criticism of this study is the high number of treatment cycles administered. This study was designed in the late 1980s, however, when the use of intravenous CMF for 9 courses of adjuvant therapy was not questioned.

The 6-year disease-free and overall survival rates for the 1,175 assessable patients were superior in all groups combined for patients treated with CEF compared with CMF (Table 4). Disease-free and overall survival rates were significantly higher for the combined groups of premenopausal patients receiving CEF compared with CMF (groups A and B). Though not statistically significant, there was trend in the postmenopausal patients (group C) in favor of CEF in terms of disease-free and overall survival. Hematologic toxicities were evenly distributed, with less than 2% of treatment cycles requiring delays of 1 week or more with either CEF or CMF. Alopecia and amenorrhea occurred more frequently in the CEF group (80% and 80%) compared with those receiving CMF (7% and 60%). Long-term toxicities of congestive heart failure and leukemia were not reported in either treatment group.

The 5-year results of a prospective randomized trial by Galligioni and colleagues<sup>24</sup> were presented at the 2000 San Antonio Breast Cancer Symposium. A regimen of high-dose epirubicin (120 mg/m<sup>2</sup>) and cyclophosphamide (EC) was compared with standard CMF in 207 high-risk premenopausal breast cancer patients with 4 or more positive lymph nodes. Although disease-free and overall survival rates favored EC, the differences were not statistically significant.

Table 4. — Results of the Danish Breast Cancer Cooperative Group Trial of CEF vs CMF<sup>23</sup>

|              |                               | Disease-Free Survival, % |     |     |         | Overall Survival, % |     |     |         |
|--------------|-------------------------------|--------------------------|-----|-----|---------|---------------------|-----|-----|---------|
|              |                               | N                        | CEF | CMF | P Value | N                   | CEF | CMF | P Value |
| Group A      | Node-negative, premenopausal  | 342                      | 84  | 78  | .09     | 343                 | 93  | 83  | <.01    |
| Group B      | Node-positive, premenopausal  | 524                      | 58  | 50  | .06     | 531                 | 66  | 60  | .2      |
| Groups A+B   | All, premenopausal            | 866                      | 68  | 60  | .01     | 874                 | 76  | 69  | .01     |
| Group C      | Node-positive, postmenopausal | 314                      | 48  | 41  | .11     | 321                 | 50  | 48  | .3      |
| Groups A+B+C | All patients                  | 1,180                    | 63  | 58  | .003    | 1,195               | 70  | 65  | .009    |

C = cyclophosphamide    M = methotrexate  
E = epirubicin            N = number of patients  
F = fluorouracil

Table 5. — Results of French Adjuvant Study Group Trial of FEC-50 vs FEC-100<sup>27</sup>

|                    | Disease-Free Survival, % |                    |         | Overall Survival, % |                    |         |
|--------------------|--------------------------|--------------------|---------|---------------------|--------------------|---------|
|                    | FEC-50<br>(n=271)        | FEC-100<br>(n=266) | P Value | FEC-50<br>(n=271)   | FEC-100<br>(n=266) | P Value |
| All patients       | 54.8                     | 66.3               | .03     | 65.3                | 77.4               | .007    |
| 1-3 positive nodes | 77.6                     | 71.0               | .42     | 83.8                | 78.2               | .63     |
| >3 positive nodes  | 49.6                     | 65.3               | .005    | 60.9                | 77.2               | .001    |

F = fluorouracil    C = cyclophosphamide  
E = epirubicin    M = methotrexate

Piccart and colleagues<sup>25</sup> reported results of a Belgian study comparing the classic oral CMF regimen with a standard- and high-dose epirubicin-based regimen in 777 premenopausal and postmenopausal women with node-positive breast cancer. The epirubicin-treated groups received 8 cycles of either standard-dose EC (60/500 mg/m<sup>2</sup>) or high-dose EC (100/830 mg/m<sup>2</sup>) every 3 weeks. At a median follow-up of 4 years, survival time between the high-dose EC group and CMF group was similar ( $P=.87$ ). A dose-response effect was observed for epirubicin as evidenced by a significant difference in event-free ( $P=.04$ ) and overall ( $P=.05$ ) survival times between high-dose EC and standard-dose EC. Outcome was also evaluated in a companion study<sup>26</sup> using stratified groups based on predictive markers, including HER2 and p53. Event-free and overall survival rates were not statistically different in HER2-positive and -negative tumors. However, there was an improved event-free survival rate in HER2-positive patients receiving high-dose EC.

These trials demonstrate activity of epirubicin-based adjuvant regimens and their superiority to (in two trials) or equivalence to (in two trials) the “gold standard” of CMF in premenopausal women with breast cancer. The epirubicin-containing regimens were associated with more grade 3 and 4 acute toxicities, such as nausea and vomiting, while a low incidence of late toxicities of congestive heart failure and acute leukemia were reported in only one of these trials. Although a direct comparison cannot be made between epirubicin-based adjuvant regimens and doxorubicin-based regimens, these results suggest that epirubicin-containing regimens produce superior results to standard CMF, in both node-positive and node-negative breast cancer.

### *Dose and Duration of Epirubicin-Based Regimens*

In order to determine the optimal dose of an epirubicin-based adjuvant regimen, the French Adjuvant

Study Group (FASG) initiated a phase III trial in node-positive operable breast cancer patients with poor prognostic factors.<sup>27</sup> Patients were randomized to receive fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy with either 50 mg/m<sup>2</sup> of epirubicin (FEC-50) or 100 mg/m<sup>2</sup> of epirubicin (FEC-100). The relative mean dose intensities of epirubicin in FEC-50 and FEC-100 were 90.3% and 86.1%, respectively. After a median follow-up time of 67 months, the disease-free and overall survival rates were significantly higher for FEC-100 compared with FEC-50 in 537 assessable patients (Table 5). In a subset analysis, this difference also translated into a significant improvement in survival for patients with >3 positive lymph nodes but not for those with 1-3 positive lymph nodes.

FEC-100 was more toxic in terms of both hematologic and nonhematologic toxicities. Grade 3 or 4 neutropenia occurred more frequently in the FEC-100 group (25.2% vs 11.1%). However, the incidence of febrile neutropenia was low (2.7%) and not associated with any treatment-related deaths. The overall risk of cardiac toxicity (1.5% and 2.1%) and the development of a secondary acute leukemia (1 lymphoid and 1 myeloid) were low for FEC-100 and FEC-50, respectively.

Dose intensity and duration of three FEC regimens were also evaluated by the FASG and reported by Fumoleau et al.<sup>28</sup> After surgery, 602 assessable premenopausal women with node-positive breast cancer were randomized to 6 cycles of FEC 50, 3 cycles of FEC 50, or 3 cycles of FEC 75. After 8 years of follow-up, no differences in disease-free survival were observed between 3 cycles of FEC 50 and 3 cycles of FEC 75. However, 6 cycles of FEC 50 produced superior disease-free survival rates compared with both 3 cycles of FEC 50 and 3 cycles of FEC 75 (55.5% vs 46.1%,  $P=.018$  and 55.5% vs 47%,  $P=.04$ , respectively). Furthermore, overall survival rates were significantly improved in patients receiving 6 cycles of FEC 50 compared with 3 cycles of FEC 50 based on a Cox regression analysis (67.4% vs 60.8%,  $P=.047$ ).

Results of these trials that have specifically evaluated dose intensity and total dose of adjuvant epirubicin are inconsistent,<sup>25,28</sup> making it difficult to draw firm conclusions on the optimal dose and duration of epirubicin as part of an adjuvant cytotoxic regimen. However, dose-intensive strategies of epirubicin are active and well tolerated. It appears that based on results of several trials of epirubicin-based adjuvant chemotherapy, epirubicin in cumulative doses of 540-720 mg/m<sup>2</sup> is necessary to attain a meaningful survival advantage.<sup>22,23,27</sup>

### Single-Agent Epirubicin in Node-Positive Breast Cancer

The ICGG conducted a phase III trial that compared the benefits of epirubicin 100 mg/m<sup>2</sup> plus tamoxifen with tamoxifen alone as adjuvant therapy of 604 postmenopausal women with axillary node-positive breast cancer.<sup>29</sup> With a median follow-up of 5.7 years, the relapse-free survival rate following treatment with the epirubicin-containing therapy was 74% compared with 62% with tamoxifen alone (*P*=.023). The relative reduction in the odds of disease recurrence associated with epirubicin plus tamoxifen was 28%. Though not statistically significant, 5-year survival rates favored epirubicin plus tamoxifen vs tamoxifen alone (81% vs 77%, *P*=.46). As expected, chemohormonal therapy was associated with a higher incidence of acute adverse effects (nausea, vomiting, alopecia, infection), but these were manageable. Long-term complications included two cases of AML and two reports of congestive heart failure. This trial is the first to report an improvement in relapse-free survival in the group of patients with single-agent adjuvant chemotherapy.

Collectively, these data support the use of epirubicin-containing chemotherapy in the adjuvant treatment of early-stage breast cancer. Regimens containing epirubicin were usually associated with longer disease-free and overall survival rates compared with standard adjuvant therapies, including CMF. The overall relative reduction in risk of relapse and risk of death among the epirubicin-containing regimens in many of these trials (Table 6) were consistently high, confirming the proportional reduction in relapse and mortality observed in the EBCTCG overview analysis. Positive effects of epirubicin have been observed in multiple subgroups of women with breast cancer including premenopausal and postmenopausal patients, patients with axillary lymph node-positive and -negative tumors, and patients with hormone receptor-positive and -negative tumors. The epirubicin-based regimens were generally well tolerated, producing manageable acute toxicities and a low incidence of long-term toxicities.

### Anthracycline-Taxane Combinations

The taxanes, paclitaxel and docetaxel, are highly effective agents in the management of breast cancer and are thus a logical choice for combining with anthracyclines. Based on the high single-agent activity in metastatic disease, incomplete cross-resistance, differing mechanisms of actions, and little overlapping nonhematologic toxicities, combining these agents is a logical step in breast cancer investigations, both in the metastatic setting and as adjuvant therapy of early-stage disease. An advantage of epirubicin over doxorubicin is the safety with which it can be combined with a taxane. Early studies evaluating the combination of doxorubicin and

Table 6. — Summary of Studies Evaluating Epirubicin-Based Adjuvant Polychemotherapy

| Study   | No. of Patients | Patient Population                                   | Regimen                  | Relative Risk Reduction, % |       |
|---|-----------------|--|--------------------------|----------------------------|-------|
|   |                 |  |                          | Relapse                    | Death |
| NCIC CTG <sup>22</sup>  | 710             | Node-positive, premenopausal                         | CEF-120 vs CMF q 4 wk    | 29                         | 19    |
| DBCG <sup>23</sup>  | 1,195           | Node-positive and -negative, pre- and postmenopausal | CEF vs CMF q 3 wk        | 27                         | 23    |
| ICCG <sup>21</sup>  | 399             | Node-positive, premenopausal                         | FEC-50 vs CMF q 4 wk     | 32                         | 46    |
| FASG <sup>27</sup>  | 565             | Node-positive  | FEC-100 vs FEC-50 q 3 wk | 27                         | 35    |
| ICCG <sup>31</sup>  | 604             | Postmenopausal                                       | E + Tam q 4 wk vs Tam    | 28                         | 12    |
| C = cyclophosphamide    M = methotrexate<br>E = epirubicin            Tam = tamoxifen<br>F = fluorouracil |                 |  |                          |                            |       |

Table 7. — Doxorubicin–Paclitaxel Combinations as First-Line Treatment of Metastatic Breast Cancer: Summary of Phase III Results

| Study   | No. of Patients | Treatment (mg/m <sup>2</sup> q 3 wk)                      | Overall Response Rate (Complete Response), % | Time to Progression, mo | Median Overall Survival, mo |
|---|-----------------|---|--|-------------------------|-----------------------------|
| Jassem et al <sup>33</sup>  | 267             | A (50) day 1 + T (220 over 3 h) day 2 vs FAC (500/50/500) | 68* (19)<br>55 (8)                           | 8.3*<br>6.2             | 23.3*<br>18.3               |
| Biganzoli et al <sup>34</sup>   | 275             | A (60) + T (175 over 3 h) vs AC (60/600)                  | 58 (NR)<br>54 (NR)                           | NR<br>NR                | NR<br>NR                    |
| * <i>P</i> < .05.<br>A = doxorubicin<br>C = cyclophosphamide<br>F = fluorouracil<br>T = paclitaxel<br>NR = not reported |                 |   |  |                         |                             |

paclitaxel demonstrated unacceptably high rates of congestive heart failure due to a pharmacokinetic interaction between the two agents resulting in an increase in the area under the concentration curve (AUC) for both doxorubicin and doxorubicinol.<sup>30,31</sup> When epirubicin is combined with paclitaxel or docetaxel, there is no effect on the AUC of epirubicin.<sup>32</sup>

### *Doxorubicin–Paclitaxel Combinations in Metastatic Breast Cancer*

Two phase III trials have evaluated the combination of doxorubicin and paclitaxel as first-line treatment of metastatic breast cancer (Table 7).<sup>33,34</sup> Jassem and colleagues<sup>33</sup> found the combination of doxorubicin and paclitaxel to be superior to standard fluorouracil, doxorubicin, and cyclophosphamide (FAC) in terms of response rate, time to disease progression, and overall survival rates. The results of a trial sponsored by the European Organization for the Research and Treatment of Cancer (EORTC)<sup>34</sup> comparing doxorubicin and paclitaxel with standard AC demonstrated that the anthracycline-paclitaxel combination was equivalent to the standard anthracycline-containing regimen. Because of these conflicting results, ongoing investigation of doxorubicin-paclitaxel combinations in the metastatic setting is needed.

### *Epirubicin–Paclitaxel Combinations in Metastatic Breast Cancer*

Two phase III trials have evaluated the combination of epirubicin and paclitaxel as first-line treatment of metastatic breast cancer (Table 8).<sup>35,36</sup> Luck et al<sup>35</sup> randomized 597 patients to either epirubicin and paclitaxel (ET) or EC as first-line therapy of metastatic disease. Overall and complete response rates were assessed in 401 patients and found to be similar between treatment groups, with a trend slightly favoring ET. Time to disease progression favored the ET, but trends in overall survival favored EC, although these differences were not significant. Although grade 3 and 4 neutropenia was a major toxicity for ET and EC (64% and 60%, respectively), febrile neutropenia was not observed.

Results of a multicenter trial performed in the United Kingdom comparing ET with EC as first-line therapy of advanced disease were recently presented.<sup>36</sup> Overall response rates were significantly higher in the ET group; however, no differences in progression-free or overall survival rates were observed. Three patients in the ET group experienced clinical cardiac toxicity compared with none in the EC group. Although a survival advantage of combining epirubicin with paclitaxel was not observed in either of these trials, it appears that ET is a

Table 8. — Epirubicin–Paclitaxel Combinations as First-Line Treatment of Metastatic Breast Cancer: Summary of Phase III Results

| Study  | No. of Patients | Treatment (mg/m <sup>2</sup> q 3 wk)     | Overall Response Rate (Complete Response), % | Time to Progression, mo | Median Overall Survival, mo |
|--|-----------------|--|--|-------------------------|-----------------------------|
| Lück et al <sup>35</sup>   | 401             | E (60) + T (175 over 3 h) vs EC (60/600) | 46 (8)<br>40 (6)                             | 9.0<br>7.4              | 16.8<br>20.3                |
| Carmichael <sup>36</sup>   | 705             | E (75) + T (200 over 3 h) vs EC (75/600) | 65* (14)<br>55 (11)                          | NR<br>NR                | 13.8<br>13.7                |
| * <i>P</i> < .05.<br>C = cyclophosphamide<br>E = epirubicin<br>T = paclitaxel<br>NR = not reported |                 |  |  |                         |                             |

Table 9. — Doxorubicin-Docetaxel Combinations as First-Line Treatment of Metastatic Breast Cancer: Summary of Phase III Results

| Study                        | No. of Patients | Treatment (mg/m <sup>2</sup> q 3 wk) | Overall Response Rate (Complete Response), % | Time to Progression, mo | Median Overall Survival, mo |
|------------------------------|-----------------|--------------------------------------|--|-------------------------|-----------------------------|
| Nabholtz et al <sup>41</sup> | 214             | A (50) + T (75) vs                   | 59* (10)                                     | 37.3 wk <sup>†</sup>    | NR                          |
|                              | 215             | AC (60/600)                          | 47 (7)                                       | 31.9 wk                 | NR                          |
| Nabholtz et al <sup>42</sup> | 238             | TAC (50/75/500) vs                   | 55* (8)                                      | NR                      | NR                          |
|                              | 237             | FAC (500/50/500)                     | 42 (5)                                       | NR                      | NR                          |

\* *P* < .01.  
† *P* < .05.  
A = doxorubicin      T = docetaxel  
C = cyclophosphamide      NR = not reported  
F = fluorouracil

feasible regimen for use in the metastatic setting. Ongoing strategies aimed at improving outcome with epirubicin-paclitaxel-based regimens include weekly administration schedules, sequential administration, and triplet combinations that include gemcitabine.<sup>37-40</sup> Investigations including new biologic agents, biphosphonates, and novel targeted therapy have to be explored as well.

### *Anthracycline-Docetaxel Combinations in Metastatic Breast Cancer*

Two phase III trials have evaluated doxorubicin-docetaxel combinations as first-line treatment of metastatic breast cancer (Table 9).<sup>41,42</sup> Doxorubicin and docetaxel were compared with standard AC as first-line therapy of 429 women with metastatic breast cancer in a phase III randomized trial reported by Nab-

holtz and colleagues.<sup>41</sup> Overall response rates and time to progression were superior in the doxorubicin-docetaxel group compared with the AC group. In a recently reported phase III trial, Nabholtz et al<sup>42</sup> compared two triplets — docetaxel, doxorubicin, cyclophosphamide (TAC) and FAC — as first-line therapy of 475 women with metastatic breast cancer. Although median time to progression was not reported and survival data were not mature, response rates were higher in the TAC group, suggesting high activity of an anthracycline-taxane regimen in patients with an unfavorable prognosis.

The epirubicin-docetaxel doublet has been evaluated as first-line or higher-line therapy of metastatic breast cancer in several phase I/II and II trials (Table 10).<sup>43-50</sup> High response rates were observed (46% to

Table 10. — Epirubicin-Docetaxel Combinations as Treatment of Metastatic Breast Cancer: Summary of Phase I/II and II Results

| Study  | No. of Patients | Treatment (mg/m <sup>2</sup> q 3 wk) | Overall Response Rate, % | Complete Response Rate, % |
|--|-----------------|--------------------------------------|--------------------------|---------------------------|
| Morales et al <sup>43</sup> (first-line)             | 88              | ET (75/75)                           | 71                       | 25                        |
| Eidtmann et al <sup>44</sup> (first-line)            | 24              | ET (90/70)                           | 70                       | 10                        |
| Estevez et al <sup>45</sup> (first- and second-line) | 21              | ET (75/75)                           | 53                       | 18                        |
| Milla-Santos et al <sup>46</sup> (first-line)        | 32              | ET (130/100) + G-CSF                 | 88                       | 34                        |
| Steger et al <sup>47</sup> (first- and second-line)  | 22              | ET (75/75)                           | 46                       | 0                         |
| Trudeau et al <sup>48</sup> (first-line)             | 33              | ET (75/60)                           | 70                       | 6                         |
| Pagani et al <sup>49</sup> (first-line)              | 68              | ET (90/75)                           | 66                       | 5                         |
| Mavroudis et al <sup>50</sup> (first-line)           | 54              | ET (70 day 1/90 day 2)               | 66                       | 9                         |

E = epirubicin  
T = docetaxel  
G-CSF = granulocyte colony-stimulating factor

88%), with neutropenia as the most common hematologic toxicity. The incidence of cardiac toxicity was low; Pagani et al<sup>49</sup> reported one case of congestive heart failure, and Milla-Santos et al<sup>46</sup> reported one case of grade 2 cardiotoxicity.

## Epirubicin-Taxane Combinations in the Adjuvant Setting

The high activity of epirubicin-taxane combinations in the metastatic setting has prompted the investigation of this combination in the adjuvant setting (Table 11). Ongoing epirubicin-taxane combination studies have varied treatment schemas including epirubicin-taxane vs a standard adjuvant regimen, adjuvant therapy vs neoadjuvant therapy, sequential epirubicin-taxane administration vs combined administration, dose-intense or dose-dense epirubicin-taxane combina-

tions vs standard regimens, and short treatment courses vs prolonged treatment courses.

## Conclusions

Epirubicin is an anthracycline that represents an advancement in breast cancer treatment. In addition to being equally effective and better tolerated than doxorubicin in women with metastatic breast cancer, epirubicin as adjuvant therapy has generally improved relapse-free and overall survival compared with standard adjuvant therapies, including CMF. The benefits of epirubicin have been observed across a range of subgroups of women with breast cancer including premenopausal and postmenopausal women, women with axillary lymph node-positive and -negative tumors, and women with either hormone receptor-positive or -negative tumors. Trials of epirubicin-based regimens in the

Table 11. — Epirubicin-Taxane Combinations as Adjuvant Therapy for Breast Cancer: Summary of Ongoing Trials

| Group   | Patient Population                                    | Treatment Regimen (mg/m <sup>2</sup> )  |
|---|---|---|
| Italian trial   | Pre- and postmenopausal, node-positive                | E (120) × 4 → CMF × 4<br>E (120) × 4 → T (100) × 4 → CMF × 4  |
| French Cooperative Group  | Pre- and postmenopausal, node-positive                | FEC (500/100/500) × 6<br>FEC (500/100/500) × 3 → T (100) × 3  |
| French Cooperative Group  | Node-positive   | FEC (500/100/500) × 6 ± trastuzumab<br>ET (75/75) × 6 ± trastuzumab   |
| International Collaborative Cancer Group  | Postmenopausal, node-positive and -negative           | E (50 days 1 and 8) × 6<br>E (50 days 1 and 8) × 3 → T (100) × 3  |
| GONO MIG-5  | Stage II, pre- and postmenopausal, 1-9 positive nodes | FEC (600/60/600) × 6<br>EP (90/175) × 4   |
| GONO MIG-7  | Stage III   | ET (75/80) × 4<br>ET (75/80) × 2 → apheresis → HDC  |
| NCIC CTG MA-21  | Node-positive or high-risk node-negative              | CEF (75/60[day 1, day 8]/500) × 6<br>EC (120/830) + G-CSF + EPO q 2 wk × 6 → P (175)<br>AC (60/600) × 4 → P (175) × 4 |
| US Community Based  | Node-positive, pre- and postmenopausal                | EC (90/600) × 4 → T or P* × 4<br>E + T or P* × 8  |
| German Intergroup   | 1-3 positive nodes                                    | EC (90/600) × 4 → T (100) × 4<br>CMF (600/40/600) × 6   |
| <p>* Taxane of choice: docetaxel 75 mg/m<sup>2</sup> or paclitaxel 175 mg/m<sup>2</sup>.<br/>           A = doxorubicin      T = docetaxel<br/>           C = cyclophosphamide      HDC = high-dose chemotherapy<br/>           E = epirubicin      G-CSF = granulocyte colony-stimulating factor<br/>           F = fluorouracil      EPO = epoetin alfa<br/>           M = methotrexate      GONO = Northwest Oncology Group in Italy<br/>           P = paclitaxel      NCIC CTG = National Cancer Institute of Canada Clinical Trials Group</p> |   |   |

adjuvant setting are ongoing, and combinations with newer cytotoxic agents such as the taxanes, trastuzumab, and bisphosphonates are also being explored in an effort to continue to improve outcomes for patients with breast cancer.

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