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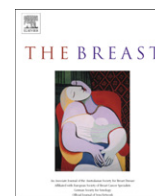
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Review

Epirubicin: Is it like doxorubicin in breast cancer? A clinical review

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ABSTRACT

Anthracyclines are among the most effective chemotherapy treatments available for various types of cancer. The anthracyclines commonly used in treatment of breast cancer are either epirubicin or doxorubicin. Epirubicin is an epimer of doxorubicin with important role in the chemotherapy treatment of both early and metastatic breast cancer. The efficacy of epirubicin is similar to doxorubicin while epirubicin has a different toxicity profile particularly in regard to cardiotoxicity. Epirubicin has been incorporated into most of the anthracycline containing chemotherapy combinations in well-conducted clinical trials involving large numbers of patients. It has also been investigated in studies involving the administration of epirubicin in dose-dense chemotherapy schedules. Short term follow up of dose-dense clinical trials demonstrated safety comparable to that of doxorubicin. This review summarizes published clinical trials investigating epirubicin in the treatment of early and advanced breast cancer.

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Introduction

Anthracyclines are a cornerstone of the standard of care of early breast cancer chemotherapy because they confer a survival advantage when compared to non-anthracycline containing adjuvant regimens.¹ The two anthracyclines, doxorubicin (Adriamycin[®]; Bedford Laboratories, Bedford, OH) and epirubicin (Ellence[®]; Pfizer Pharmaceuticals, New York), have formed the backbone of most combination chemotherapy regimens in early breast cancer clinical trials and hence they are the two most commonly used anthracyclines in clinical practice.^{1,2}

For decades, optimization of scheduling and evaluation of the anthracyclines in combination regimens had been a central focus of clinical investigation. The breast cancer community outside the U.S. began using epirubicin in the 1980s. In the U.S. however, use of epirubicin was delayed until the U.S. Food and Drug Administration

approved it for the adjuvant treatment of breast cancer in 1999. The subsequent addition of the taxanes and trastuzumab, the latter for human epidermal growth factor receptor 2 (HER2) overexpressing patients, further improved the efficacy of systemic therapies in studies involving patients with high-risk early breast cancer.³

The serious cumulative toxicities of the anthracyclines are the minimal risk of cardiotoxicity and secondary leukemia. Trastuzumab is also cardiotoxic, albeit mediated by a different mechanism, and the risks of cardiotoxicity are higher in patients who have received an anthracycline.⁴ As a result some treatment regimens have been developed without an anthracycline. These are taxane based, and their use has been promoted on the basis of cardiac safety.^{5,6} However, the use of a non-anthracycline based regimen may not be adequate in the high-risk population. There are data directly comparing epirubicin and doxorubicin head-to-head in metastatic breast cancer (MBC) and also in the adjuvant setting.⁷ Findlay *et al.* have shown that in the metastatic setting at equimolar doses, epirubicin is therapeutically equivalent to doxorubicin, but has a more favorable toxicity profile, including cardiac and hematologic toxicity compared to doxorubicin.^{8,9}

Search strategy and selection criteria

References for this Review were identified through searches of ISI web of Science and PubMed (from 1970 until June 21, 2011), The Cochrane Library (from 1970 until June 21, 2011), and Scopus (from

Abbreviations: A, Adriamycin (doxorubicin); AML, Acute Myeloid Leukemia; ALL, Acute Lymphocytic Leukemia; C, cyclophosphamide; D, docetaxel; DFS, Disease Free Survival; E, epirubicin; EFS, Event Free Survival; F, fluorouracil; FN, Febrile neutropenia; HER2, human epidermal growth factor receptor 2; ICCG, International Collaborative Cancer Group; M, methotrexate; MBC, metastatic breast cancer; NEAT, National Epirubicin Adjuvant Trial; OS, Overall Survival; P, Paclitaxel; RFS, Relapse Free Survival; EBCTCG, The Early Breast Cancer Trialists' Collaborative Group.

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1970 until June 21, 2011). Medline MeSH subject headings used were “Epirubicin”, “Breast Cancer”, “clinical trial”, “Early Breast Cancer”.

“Metastatic Breast Cancer”, “Anthracycline”, combined with various keywords limiting the search to breast cancer and clinical trial. The last search was done on June 21, 2011. Searches in PubMed were limited to clinical trials, meta-analyses, practice guidelines, randomized control trials, guidelines, systematic reviews, and reviews (published in English). Reference lists of retrieved articles were then searched to identify other relevant publications. The “Related articles” feature of PubMed was also used to identify other relevant publications. Review articles in the bibliography provided additional citations in the literature.

Web of Science® – with Conference Proceedings was searched to retrieve abstracts from relevant conferences including the annual meetings of the American Society of Clinical Oncology up to the meeting of June 2011, the San Antonio Breast Cancer Symposium and the European Society of Medical Oncology up to the meetings of 2010.

Characteristics of epirubicin

Epirubicin is a 4'-epimer of doxorubicin; the difference with the latter is in the reorientation (epimerization) of the hydroxyl group in the 4' position of the daunosamine ring (Fig. 1). Epirubicin was approved in France in 1982 and during the last 15 years, has been the subject of more than 2000 publications that have characterized its efficacy and safety through clinical trials and post-marketing surveillance studies in more than a million patients. Epirubicin is now marketed in more than 80 countries for the treatment of breast cancer and a variety of other malignancies. The mechanism of action of epirubicin is through intercalation of DNA, inhibition of topoisomerase II activity, generation of oxygen and drug free radical, with consequent interference with DNA, RNA, and protein synthesis and its cytotoxic activity that are also implicated in the mechanism of cardiac toxicity of doxorubicin and other anthracyclines.¹⁰

Epirubicin in metastatic breast cancer

Because epirubicin can be given at higher cumulative doses before causing cardiotoxic effect, higher doses of this anthracycline were studied and when compared with lower epirubicin doses, led to improved response rates.^{9,11,12} The Cancer Care Ontario Practice Guidelines Initiative developed evidence-based guidelines to provide a rationale for the choice between doxorubicin and epirubicin and to make recommendations regarding the dose of epirubicin.⁸ They identified randomized controlled trials comparing epirubicin and doxorubicin in metastatic breast cancer, either as

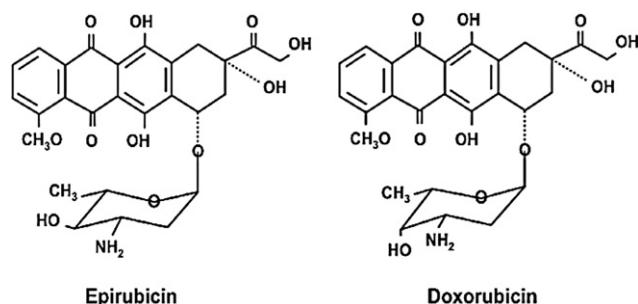


Fig. 1. Epirubicin is a 4'-epimer of doxorubicin; the difference is in the reorientation (epimerization) of the hydroxyl group in the 4' position of the daunosamine ring.

Table 1
Studies of epirubicin- versus doxorubicin-based therapies in the metastatic setting.

| Trial | N | Treatment group | RR % | mOS months |
|---|-----|-----------------|------|------------|
| FAC vs. FEC | | | | |
| French (1988) ¹³ | 113 | FAC-50 | 52 | 17.0 |
| | 117 | FEC-50 | 50 | 15.0 |
| Italian (1988) ¹⁴ | 221 | FAC-50 | 56 | 20.0 |
| | 222 | FEC-50 | 54 | 19.0 |
| Lopez (1989) ¹⁵ | 46 | FAC-50 | 46 | 16.0 |
| | 48 | FEC-50 | 44 | 14.0 |
| Doxorubicin and epirubicin at equal doses | | | | |
| Heidemann (1990) ⁶² | 51 | AC-40 | 42 | NR |
| | 66 | EC-40 | 42 | NR |
| Lawton (1993) ⁶³ | 28 | A-70 | 36 | ≈ 8 |
| | 28 | E-70 | 32 | ≈ 10 |
| Gasparini (1991) ⁶⁴ | 21 | A-20 | 38 | 11 |
| | 22 | E-20 | 36 | 12 |
| Castiglione (1990) ⁶⁵ | >50 | A-20 | 29 | 15 |
| | >50 | E-20 | 20 | 13 |

single agents or as part of combination chemotherapy. Outcomes of interest were response rate, median survival, and toxicity. Eleven published reports and 2 abstracts were selected as being relevant to the topic. The studies were grouped according to dosage, and 7 studies with epirubicin and doxorubicin at equal doses were identified. Epirubicin was given as single agents in three trials and as part of multi-agent chemotherapy in four trials. There was no significant difference in tumor response rate or survival between these two agents at equal doses (Table 1).^{13–15} These guidelines have not been updated recently and are currently archived [personal communication with the Program in Evidence-Based Care, McMaster University, Ontario, Canada].

The meta-analysis of epirubicin and doxorubicin for survival data in the trials evaluating escalating epirubicin doses included published reports of five trials and response data for six trials available for the Canadian guideline developers.⁸ There was no difference in the pooled one-year survival rates (risk ratio for mortality, 1.01; $p = 0.87$) or response rate (risk ratio, 1.04; $p = 0.51$).⁸ Similarly, randomized trials compared epirubicin at a higher dose to doxorubicin (as single agents in four trials and as part of multi-agent chemotherapy in one trial) detected no significant differences between these two agents in response rate or survival.⁸ When epirubicin was given at escalating doses, significantly higher response rates were observed with the higher doses of epirubicin as a single agent or part of a multi-agent chemotherapy in randomized trials. However, no differences in survival were observed between doses (Table 2).^{11,12,16}

Epirubicin toxicity

In clinical trials comparing equimolar doses of epirubicin and doxorubicin, epirubicin yielded less myelosuppression, fewer

Table 2
Studies of escalating doses of epirubicin in the metastatic setting.

| Trial | N | Treatment group | RR % | mOS m |
|--------------------------------|-----|-----------------|-----------------|-------|
| Focan (1993) ¹¹ | 71 | FEC-50 | 41 ^a | 24 |
| | 70 | FEC 100 | 69 | 27 |
| Habeshaw (1991) ¹² | 104 | E-50 | 23 ^b | 10.6 |
| | 105 | E-100 | 41 | 10.1 |
| Bastholdt (1996) ¹⁶ | 75 | E-40 | 20 ^b | 13.6 |
| | 66 | E-60 | 19.7 | 14.0 |
| | 64 | E-90 | 37.5 | 14.6 |
| | 58 | E-135 | 36.2 | 11.3 |

^a $P < 0.001$

^b $P < 0.01$.

reported non-hematologic toxicities (nausea/vomiting, alopecia, mucositis), and cardiac (electrocardiographic changes with or without clinical congestive cardiac failure) toxicities.⁷ The equitoxic dose ratios of doxorubicin to epirubicin for myelosuppression and cardiotoxicity are 1:1.2 and 1:1.7–2.0, respectively.¹⁷ The results of the 7 studies comparing the two anthracyclines (at equimolar doses) were pooled and analyzed. There was less nausea and vomiting with epirubicin compared to doxorubicin (risk ratio, 0.76; $p = 0.004$), less neutropenia (risk ratio, 0.52; $p = 0.001$), and cardiac toxicity (risk ratio, 0.43; $p = 0.004$). There were also fewer episodes of heart failure (risk ratio, 0.38; $p = 0.05$).⁸ The probability of developing clinically evident congestive cardiac failure is estimated as approximately 0.9% at a cumulative dose of 550 mg/m², 1.6% at 700 mg/m², and 3.3% at 900 mg/m². The risk of congestive cardiac failure increases rapidly with increasing cumulative doses in excess of 900 mg/m².¹⁸ The cumulative epirubicin cardiac toxicity across all trials are less than 1%–2.5% (Tables 3,4) which is similar to the rates observed in studies using doxorubicin.^{19–24}

Epirubicin has been favored over doxorubicin and used with concurrent trastuzumab in some ongoing studies because of its lower cardiac toxicity profile.^{25,26} However it is not recommended to give anthracycline concurrently with anti-HER2 therapy, such as trastuzumab, due to the concerns for increased late cardiac toxicity. Indeed, a study was conducted in 45 patients, 23 had prior anthracyclines. Epirubicin 90 mg/m² was given every 3 weeks plus weekly trastuzumab at 2 mg/kg loading dose, then 1 mg/kg for 6/8 cycles, followed by single agent trastuzumab. Median survival was 32.8 months. Two (4.5%) patients developed CHF. The authors concluded that the relatively high rate of cardiotoxicity together with the availability of less cardiotoxic and active trastuzumab-containing combinations cannot justify further evaluation of this regimen.²⁷

No studies so far, comparing doxorubicin directly to epirubicin, have reported data on quality of life. However authors of the

Mammary 21 (MA 21) study indicated that the quality of life data will be released in subsequent publication.⁷

Liposomal or pegylated formulations of doxorubicin are used in metastatic breast cancer²⁸ but not in the adjuvant setting. A study randomised 160 women with metastatic breast cancer randomised to non-pegylated liposomal doxorubicin (75 mg/m²) or epirubicin (75 mg/m²) combined with cyclophosphamide 3 weekly for up to eight cycles. Differences in response and survival were not statistically significant. Neutropenia and stomatitis/mucositis were less common in patients who received epirubicin.²⁹

Epirubicin in breast cancer in the adjuvant setting

The optimal combination, dosing, and schedule of chemotherapy in early breast cancer collectively is an area of continuing investigation and ongoing debate.

Although standards of care can be varying but adjuvant chemotherapy in 2011 is generally recommended in women with TNBC and HER-2 amplified tumors. In women with hormone receptor positive tumors, it is reserved for tumors that are large or with extensive nodal involvement or high-risk biology such as young age, lymphovascular space invasion, have a high proliferative index (Ki67 expression), lower ER/PR expression, higher Oncotype Dx score or luminal B tumors.³⁰

Trials have been conducted comparing many different schedules and doses of the anthracyclines in the adjuvant setting (Table 3). A PubMed search for doxorubicin on June 21, 2011 in the adjuvant breast cancer setting yielded 1876 publications compared to 721 for epirubicin and the figures were 779 compared to 328 when the search was limited to clinical trials. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of adjuvant treatment for breast cancer included both doxorubicin-treated (60%) and epirubicin-treated (40%) patients.³¹ In several countries in Europe, Australia, and Canada, epirubicin was commonly studied

Table 3
Clinical trials of epirubicin in the adjuvant setting.

| Study | N | F/U | Chemo regimes and doses | Total Epi (mg/m) | FN | AML/ALL | CHF cardiac death | DFS/EFS/RFS | OS |
|---|---------------------------------|-----|--------------------------------------|------------------|---------------|------------------------|----------------------------|---------------|-----------|
| MA 5 (Levine JCO 2005) ³⁶ | 710 | 10 | CEF × 6, (po 75 + 60/500 d 1 + 8) | 720 | 8.5% | 1.4% | 1.1% | 52% | 62% |
| | | y | Classical CMF × 6 | | 1.1% | 0.2% | 0.2% | 45%* | 58%* |
| FASG 05 (Bonnetrrre JCO 2005) ³³ | 565 | 67 | FEC 100 × 6, (500/100/500) | 600 | 2.5% | 0.3% | 1.1% | 66% | 77% |
| | | mo | FEC 50 × 6, (500/50/500) | 300 | 0% | 0.3% | 0% | 55%* | 65%* |
| PACS 01 (Coudert SABC 2009) ³⁹ | 1999 | 93 | FEC 100 × 3-D × 3, | 300 | 11.2% | 0.2% | 0% | 70% | 83% |
| | | mo | (500/100/500)-(100) | 600 | 8.4% | 0.4% | 0.4% | 66%* | 78%* |
| | | | FEC 100 × 6, (500/100/500) | | | | | | |
| MA 21 (Burnell JCO 2010) ⁷ | 2104 | 30 | CEF × 6, (75 + 60/500 d 1+8) | 720 | 22.3% | 0.6% | 2.5% | 90.1% | NR |
| | | mo | dd EC × 6-P × 4, (120/830)-(175) | 720 | 16.4% | 0.6% | 1.0% | 89.5% | |
| | | | ACP q 3 w, (60/600)-(175) | | 4.8% | 0% | 0.6% | 85% | |
| | | | | | | | | CEF > ACP* | |
| | | | | | | | | ddECP > ACP* | |
| | | | | | | | | CEF = dd EC-P | |
| NEAT/BR9601 (Poole NEJM 2006) ⁴⁰ | 2391 | 48 | E100 × 4-CMF × 4 | 400 | 14% | NR | NR | 76% | 82% |
| | | mo | CMF × 6–8 | | 11% | | | 69%* | 75%* |
| | | | | | | | | (NEAT) | |
| GEICAM 9906 Martin JNCI 2008) ⁶⁶ | 1246 | 66 | FEC × 4-w P × 8, | 360 | 5% | NR | 0% | 79% | 90% |
| | | mo | (600/90/600)-(100) | 540 | 9.5% | | 0.8% | 72%* | 87% |
| | | | FEC × 6, (600/90/600) | | | | | | |
| Piccart JCO 2001) ⁴² | 777 | 4 | Classical CMF × 6 EC 60 × 8, 60/500) | 480 | NR | 0% | 0% | CMF = HEC | CMF = HEC |
| | | y | HEC100 × 8, (100/830) | 800 | | 0% | 0.4% | HEC > EC* | HEC > EC* |
| | | | | | | 1.2% | 1.2% | | |
| PACS 04 (Roche SABC 2009) ⁴¹ | 3010 | 59 | ED × 6, (75/75) | 450 | 31.5% | 0.06% | 0.3% | 82% | 90% |
| | | mo | FEC 100 × 6, (500/100/500) | 600 | 10.7% | 0.3% | 0.3% | 80% | 90% |
| The Danish Breast Cancer Group) ³⁷ | 1224 (CMF n = 615; CEF n = 584) | 10 | CEF vs. CMF | 540 | none reported | 1 AML in each group | CEF (0.68%) and CMF (0.4%) | DFS | 62% |
| | | yr | | | | 1 MDS in the CMF group | | | 55% |

*ACP: Doxorubicin and cyclophosphamide (AC) followed by Paclitaxel.

Table 4
Clinical trials of dose-dense epirubicin-based chemotherapy.

| Study | N | F/U | Chemo regimes and doses | Tot Epi (mg/m) | FN | AML/ALL | CHF cardiac death | DFS/EFS/RFS | OS |
|---|-----|-------|---|------------------------------|-----------------------|------------|-------------------|------------------|------------|
| EORTC/NCIC/SAKK (Therasse JCO 2003) ⁴⁵ | 448 | 5.5 y | CEF × 6, (po 75 + 60/500 d 1+8) dd EC × 6, (120/830) | 720 720 | 14% 8.4% | 0% 0.5% | 0.9% 0.9% | Med PFS 34 mo | 53% 51% |
| dd FEC-Taxanes (Dang CCR 2004) ⁴⁶ | 44 | NR | dd FEC 100 × 6-P/D × 18 (500/100/500)-80/35 | 600 | 5% | NR | NR | NR | NR |
| dd EC-dd P (Dang CBC 2008) ⁴⁷ | 38 | 34 mo | dd EC100 × 6- dd P × 6, (100/600)-(175) | 600 | 16% | NR | 2.6% | NR | NR |
| dd EC-dd P (Fornier CCR 2007) ⁴⁸ | 39 | 21 mo | dd EC × 4-, dd P × 4 q 10-11 d, (100/600)-(175) | 400 | 16% | NR | NR | 100% | 100% |
| dd EC-DX (Nieto Cancer Chemo Pharm 2010) ⁴⁹ | 55 | 48 mo | dd EC × 4-DX × 4, (100/600)- (75/1000 BID) | 400 | 9% (dd EC) 5% (DX) | NR | 0% | 91% | 98% |
| SBG 2004-1 Tailored vs fixed dose (Margolin Acta Oncol; 2011) ⁵⁰ | 124 | NR | A. Tailored dd EC-/T, (38-60-75-90-105-120/450-600-900-1200/60-75-85-100) B. Fixed dose-dense EC/T (E 90/600/75) C. TAC (75/50/500) | A. 381* B 357* C. 357* | 24% 5% 15% | NR | NR | NR | NR |

Statistically Significant, E = epirubicin, F = fluorouracil, C = cyclophosphamide, M = methotrexate, D = docetaxel. FN = Febrile neutropenia; AML = Acute Myeloid Leukemia; ALL = Acute Lymphocytic Leukemia; DFS = Disease Free Survival, OS = Overall Survival; RFS = Relapse Free Survival, EFS = Event Free Survival.

* Mean cumulative dose of epirubicin per patient.

in the adjuvant setting. This was based on a series of large phase III clinical trials comparing various anthracycline chemotherapy containing regimens as well as cyclophosphamide, methotrexate, and fluorouracil (CMF) in both node-positive and node-negative breast cancer patients.

The International Collaborative Cancer Group (ICCG) performed a large randomized trial comparing two different fluorouracil, epirubicin and cyclophosphamide (FEC) regimens with two different CMF regimens in node-positive premenopausal women. This trial found evidence of longer overall survival (OS) ($p = 0.02$) and relapse free survival (RFS) ($p = 0.03$) with six-cycles of FEC compared with a six-cycle CMF combination.³² The French Adjuvant Study Group (FASG) conducted a series of clinical trials building on results of earlier studies. The FASG 05 trial of combination chemotherapy in node-positive breast cancer patients with hormone receptor-negative patients compared epirubicin at doses of 50 mg/m² (FEC 50) with 100 mg/m² (FEC 100).³³ The 5 year follow-up analysis showed significant advantages for the FEC 100 regimen in disease free survival (DFS) (66.3% versus 54.8%; $p = 0.03$) and OS (77.4% versus 65.3%; $p = 0.007$).³³ A 10-year follow-up revealed the superiority of six cycles of FEC 100 in terms of DFS (50.7% versus 45.3%), with a relative risk reduction of 24%, and similar results in terms of OS (54.8% versus 50.0% in favor of FEC 100).³⁴ The FASG 05 trial demonstrated a dose-response effect of epirubicin, as increasing the dose from 50 mg/m² to 100 mg/m² in the FEC regimen resulted in longer DFS and OS.

The National Cancer Institute of Canada (NCIC) in the Mammary 5 (MA.5) study also evaluated both moderate-risk (1–3 positive nodes) and high-risk (≥ 4 positive nodes) premenopausal women receiving either cyclophosphamide, epirubicin, 5-fluorouracil (CEF) or CMF. The CEF regimen was superior to CMF with 63% 5-year relapse-free survival in the CEF, compared with 53% of the CMF group ($p = 0.009$), and OS rates were 77% and 70%, for CEF and CMF respectively ($p = 0.03$).³⁵ The 10-year RFS was 52% for patients who received CEF compared with 45% for CMF patients ($P = 0.007$). The 10-year OS for patients who received CEF was 62% compared to 58% with CMF ($P = 0.085$). The original publication at 5 years of follow-up reported that 5 patients in the CEF group experienced acute leukemia (1.5%). This did not change with further follow up but one patient in the CMF group experienced leukemia (<1%). The rate of congestive heart failure (CHF) was slightly higher [4 patients (1.1%)] in the CEF group vs. [1 patient (0.3%)] in the CMF group.³⁶ Both the FASG 05 and the NCIC MA.5 trials showed the benefit of optimal dosing of epirubicin in the polychemotherapy regimen to achieve better long-term 10-year outcomes in high-risk node-positive breast cancer.^{34,36} The Danish Breast Cancer Group also obtained

similar results, where survival at 6 years was 93% in the node-negative patients who received CEF (with 60 mg/m² epirubicin), compared with 83% in those who received CMF ($p < 0.01$).³⁷

Nitz et al randomized 2011 lymph nodes positive patients to a phase III trial comparing 4 cycles of 3 weekly EC (epirubicin and cyclophosphamide) with 100 mg/m² of epirubicin followed by 4 cycles of 3 weekly Docetaxel (D) 100 mg/m² ($n = 1008$) versus a control arm of 6 cycles of 3 weekly FEC ($n = 828$) or CMF given on day 1 and 8 every 4 weeks ($n = 175$).³⁸ After a median follow up of 41 months, both event free survival (EFS) and OS were significantly better in the EC- docetaxel arm. This confirmed superiority of sequential EC- docetaxel in terms of EFS and OS over FEC 100 in an intermediate risk group.³⁸ However, severe adverse events have been reported in 198 patients in the EC/docetaxel arm compared to 114 in CEF/CMF patients.³⁸

In 2009 an update of the PACS 01 study with 6 cycles of FEC 100 (5FU/epirubicin/cyclophosphamide 500/100/500 mg/m² every 3 weeks), or 3 cycles of FEC 100 followed by 3 cycles of docetaxel (D) 100 mg/m² every 3 weeks was reported. Eight-year DFS rates were 65.8% with FEC and 70.2% with FEC-D. There was a 15% reduction in the relative risk of relapse with FEC-D ($p = 0.03$). OS rates at 8 years were 78% with FEC and 83.2% with FEC-D.³⁹

The National Epirubicin Adjuvant Trial (NEAT) and the Scottish Cancer Trials Breast Group BR9601 trials compared 2 regimens of CMF against epirubicin followed by CMF (E-CMF). A planned pooled efficacy analysis was conducted.⁴⁰ E-CMF produced significantly better RFS at 2 and 5 years (91% versus 85% at 2 years; 76% versus 69% at 5 years, $P < 0.001$ for all comparisons). The OS was also better in the epirubicin arm with a survival rate of 95% versus 92% at 2 years; 82% versus 75% at 5 years ($P < 0.001$). This was irrespective of nodal status, and it was noteworthy that 28% of the 2391 patients enrolled in the two studies were node-negative.⁴⁰

These trials demonstrated that epirubicin (100 mg/m²), when substituting a part of a CMF combination chemotherapy in the adjuvant breast cancer setting, led to superior RFS and OS when compared to CMF alone.

In the majority of the trials discussed above where the epirubicin containing regimens were superior to the comparators, the dose of epirubicin per cycle was at least 90 mg/m² (Table 3). The few studies that did not consistently show superiority involved epirubicin at doses less than 90 mg/m². One such study was PACS 04 in which epirubicin and docetaxel 75 mg/m² (ED 75) was not better than FEC 100 in efficacy outcomes.⁴¹

Another trial was by Piccart et al that showed a dose-response relationship with epirubicin. In this study full-dose epirubicin (100 mg/m²) with cyclophosphamide (HEC100) was equal to

classical CMF and HEC100 was superior to moderate-dose epirubicin (60 mg/m²) with cyclophosphamide regimen (EC 60). This study was not set up to compare EC60 to CMF, and thus it is unknown if EC60 was inferior to CMF.⁴²

In a retrospective study of HER2-positive breast cancer and treated with a neoadjuvant regimen, sequential paclitaxel and trastuzumab and FEC-75 in combination with trastuzumab achieved a significantly higher pCR rate compared to TCH (docetaxel, carboplatin and trastuzumab). TCH was also inferior in terms of 3-year RFS rates 71% vs. 93% ($P < 0.001$), and OS rates of 86% vs. 96% ($P = 0.008$). No significant differences were noted in cardiotoxicity.⁴³ There were however, only a small number of events in both groups.

Dose-dense (dd) epirubicin for early breast cancer

Treatment outcomes in breast cancer are influenced by the successful delivery of the intended doses of chemotherapy on schedule. Optimal dose intensity in combination chemotherapy requires maintaining both meticulous dose level and schedule. Dose-dense schedules are achieved by shortening the interval between cycles and this is based on the hypothesis that shorter intervals between chemotherapy treatments could result in a higher log-kill, thus leading to lower relapse rates and longer survival times.⁴⁴

Myelotoxicity historically limited dose density but it became possible with the availability of the cytokine granulocyte colony-stimulating factor (G-CSF) to modify chemotherapy-induced neutropenia. This allows chemotherapy to be scheduled every 2 weeks instead of every 3 weeks. Dose-dense (dd) doxorubicin regimens have been extensively studied.⁴⁴ For epirubicin, several trials have reported on dose-dense combination (Table 4) with cyclophosphamide (EC) and dose-dense fluorouracil, epirubicin and cyclophosphamide (FEC) in 3–6 cycles with epirubicin doses at 75–120 mg/m²⁴⁵; dd FEC-Paclitaxel (P) alternating with Docetaxel (D)⁴⁶ dd EC-dd Paclitaxel,⁴⁷ dd EC-dd Paclitaxel⁴⁸; dd EC-Docetaxel and Capecitabine⁴⁹; SBG 2004-1: Tailored vs fixed dose with 3 arms: tailored dd EC- docetaxel, fixed dose-dense EC- docetaxel and TAC (docetaxel, doxorubicin and cyclophosphamide).⁵⁰

A randomized Phase II study compared safety and relative toxicity of AC vs EC given by conventional or dd schedules as neoadjuvant or adjuvant chemotherapy.⁴⁶ A total of 126 patients were randomized: 42 to AC (cyclophosphamide 600 mg/m² with doxorubicin 60 mg/m²) every 3 weeks, 42 to dd AC, 19 with EC (90 mg/m² epirubicin) every 3 weeks, and 23 with dd EC. A trend toward more neutropenic fever was seen in the combined standard and accelerated AC arms (12/84, 14%) compared to the combined EC arms (1/42, 2%), $p = 0.06$. Left ventricular ejection fraction drops were not increased with dd therapy.⁵¹

Nieto et al reported on 4 cycles of dd EC (epirubicin 100 mg/m² and cyclophosphamide 600 mg/m²) with G-CSF on days 3–10, followed by 4 cycles of docetaxel/capecitabine (75/1000 mg/m² b.i.d., days 1–14) every 3 weeks.⁴⁹ The incidence of febrile neutropenia was 9% during the dose-dense EC compared to 5% during docetaxel and capecitabine. Dang et al reported a study of dd EC (epirubicin at 100 mg/m²) × 6 cycles followed by dd paclitaxel × 6, and all cycles were given with pegfilgrastim (31). Fornier et al reported on a shorter duration of therapy with dd EC (epirubicin at 100 mg/m²) × 4 followed by dd paclitaxel × 4, all given every 10–11 days apart with G-CSF (31–32). Both studies were reported the regimens to be feasible. However, the incidence of febrile neutropenia (FN) was 16% in both.^{47,52} On the other hand, Dang et al also reported on dd FEC (epirubicin at 100 mg/m²) × 6 followed by 18 weeks of weekly paclitaxel alternating with docetaxel and the FN rate was only 5%.⁴⁶ Now with longer follow-up for dd FEC-weekly taxane study (at 5 years) and dd EC × 6-dd paclitaxel × 6

(at 8 years), the incidence of grades 3–4 congestive heart failure (CHF) collectively was 2.4%.⁵³ This certainly suggested that the long-term incidence of cardiac events of dd epirubicin-based treatments appeared similar to that of conventionally every 3–4 week schedules of ≤2.5% (Table 3).

A number of German phase trials studied epirubicin containing dose-dense adjuvant chemotherapy. A multi-center phase-III trial of the German AGO Group published last year and updated this year randomized 1284 patients to either 3 biweekly cycles of epirubicin (150 mg/m²), paclitaxel (225 mg/m²) and cyclophosphamide (2500 mg/m²) (idd ETC) with G-CSF support. The control arm received 4 cycles of epirubicin/cyclophosphamide (90/600 mg/m²) followed by 4 cycles of paclitaxel (175 mg/m²), all given every 3 weeks. The eight-year follow-up reported no severe late cardiotoxicity. In the idd ETC-Arm, 8 patients developed AML or MDS and no cases occurred in the control arm. The RFS and OS were 62% and 71% in the idd ETC-arm vs. 51% and 65% in the standard arm.^{54,55}

The other German study investigated 4 cycles of dose-intensified epirubicin 120 mg/m² monotherapy every 3 weeks (E120; $n = 202$) or 4 cycles of epirubicin 90 mg/m² plus cyclophosphamide 600 mg/m² (EC) every 3 weeks followed by three cycles of CMF every 4 weeks (EC-CMF; $n = 209$) in patients with primary breast cancer and 10 or more involved axillary nodes. At 5 years, the data demonstrated that 4 cycles of dose-intensified epirubicin monotherapy could be as effective as 7 cycles of standard sequential polychemotherapy in this population with EFS rates of 47.7% for E120 and 45.9% for EC-CMF. The E120 regimen was as effective as EC-CMF with regard to 5 year OS rates, 64.1% in the E120 group versus 63.5% in the EC-CMF group.⁵⁶

In a head to head comparison of adjuvant epirubicin with docorubicin regimens, Burnell et al. showed that AC followed by paclitaxel (ACP; $n = 702$) is significantly inferior to CEF or dose-dense EC followed by paclitaxel dd EC-P; ($n = 701$) in terms of RFS in node-positive and high-risk node-negative breast cancer. Safer cardiotoxicity profile allowed planning higher doses of epirubicin (120 mg/m²) compared to the doxorubicin (60 mg/m²) arm. Three-year RFS rates for CEF, EC/T, and AC/T were 90.1%, 89.5%, and 85.0%, respectively. The toxicities of the regimens were different as ACP had a febrile neutropenia rate of only 4.8%, whereas the rates were 22.3% with CEF and 16.4% with dd EC-P.⁷ Of note, the use of G-CSF was mandatory in the dd EC-P and optional in CEF patients.

A Scandinavian 3 arm phase III study (SBG 2004-1) also concluded that dose-dense and tailored EC-P can be given with manageable toxicity.⁵⁰ Survival and long-term toxicity data were not reported in that study. Another Scandinavian study (SBG 2000-1), enrolled 1535 patients treated with standard FEC and then on the basis of WBC nadirs, 524 were randomized to tailored FEC and 528 to standard FEC. The registered group consisted of 401 patients with grade 3–4 leucopenia whom received standard FEC and reported feasible results after 5.8 years but no statistically significant improvement in efficacy of tailored dosed FEC was seen compared with standard BSA based FEC.⁵⁷

In the US there was a recent shortage of doxorubicin. In some markets this shortage has become acute. Thus, in the adjuvant treatment of breast cancer 4 cycles of EC were used in place of AC × 4. The doses of epirubicin were 90–100 mg/m², given every 2–3 weeks apart; G-CSF was used when EC was given in a dose-dense schedule [personal communication; MK and CD]. Doxorubicin has been less expensive than epirubicin. However cost is less likely to remain an issue in the future because epirubicin has recently become generic. Based on the existing data, the dose of 90–100 mg/m² of epirubicin is appropriate to replace doxorubicin at 60 mg/m². Previous studies showed that epirubicin-based regimens were superior to the comparators when the dose of this anthracycline was at least 90 mg/m²/cycle.

Primary systemic therapies

Both doxorubicin and epirubicin have been used in the primary/neo-adjuvant setting, and both have been used with concurrent trastuzumab. The NeOAdjuvant Herceptin (NOAH) study used AP with concurrent trastuzumab while the Geparquinto (A phase III trials program exploring the integration of bevacizumab, everolimus (RAD001), and trastuzumab and lapatinib into current neoadjuvant chemotherapy regimens for primary breast cancer) and NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) studies utilized epirubicin in combination with anti-HER2 agents. These regimens were associated with high pathologic complete response (pCR) rates. Follow-up is relatively short but so far, reported cardiotoxicity is low. However, it is premature to accept that epirubicin can be given safely with trastuzumab concurrently due to an inadequate long-term follow-up. There are controversies in the management of HER2(+) breast cancer and optimal chemotherapy with trastuzumab is an area of ongoing research activity.⁵⁸

Longer follow-up of these cohorts will inform the long-term cardiac safety of these concurrent anthracycline-trastuzumab regimens. To the best of our knowledge, no direct comparisons of the competing anthracyclines combined with concurrent anti-HER2 therapy have been conducted. Recently reported neoadjuvant studies include the BEVERLY 2 study that was designed to evaluate bevacizumab in combination with chemotherapy (FEC-docetaxel) and trastuzumab in patients with HER2-positive inflammatory breast cancer ($n = 52$). The pCR rate was 63.5% (95% CI 49.4–77.5%) but 73% of patients experienced grade 3 toxicity during neoadjuvant treatment and there were 3 grade 2 congestive cardiac failures observed.⁵⁹

Chemotherapy-related cardiac dysfunction are described as either type I or type II.⁶⁰ Type I reflects the scenario of damage associated with myocyte death while Type II is more benign and is associated with what is described as cell hibernation or myocardial stunning. Anthracycline-associated abnormalities and their related cardiac dysfunction constitute an entity that is considered type I which is due, at least in part, to iron-based oxygen free-radical-induced oxidative stress on cardiac muscle cells. Free radicals induce the peroxidation of myocyte membranes and subsequent influx of intracellular calcium. Mitochondrial dysfunction also has been noted with and correlates with morphologic changes seen in type I.⁶⁰ Type II cardiac dysfunction has been described with trastuzumab. The molecular basis of type II with trastuzumab may be related to it binding to the extracellular domain of the HER-2 protein and inhibiting ErbB2 signaling required for the growth, repair, and survival of cardiomyocytes.⁶¹

Conclusions

Epirubicin is an important cytotoxic agent in the chemotherapy armamentarium for the treatment of both early and metastatic breast cancer. Evidence suggests that at equimolar doses, the efficacy of epirubicin is similar to doxorubicin while epirubicin has a more favorable hematologic and non-hematologic toxicity profile, particularly regarding cardiotoxicity. This permitted administration of higher doses of epirubicin up to 90–100 mg/m² compared to 60 mg/m² of doxorubicin without evident additional cardiac toxicity, especially in the adjuvant treatment of breast cancer.

While this review is summarizing the literature and not advocating the use of epirubicin over doxorubicin; epirubicin has been incorporated into most of the standard chemotherapy combinations in well-conducted clinical trials involving large numbers of patients. The efficacy and safety of concurrent use with anti HER-2 agents continues to be explored. It has also been investigated in

studies involving the administration of epirubicin in dose-dense chemotherapy schedules with feasibility and acceptable short and long-term cardiac safety.

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