Commentary: Anthracyclines in Early-Stage Breast Cancer: Is It the End of an Era?

KATHLEEN I. PRITCHARD\textsuperscript{a,b}

\textsuperscript{a}Sunnybrook Odette Cancer Centre, Toronto, Canada; \textsuperscript{b}University of Toronto, Toronto, Canada

Disclosures: Kathleen I. Pritchard: Consultant/advisory role: Novartis, Roche, AstraZeneca, GlaxoSmithKline, Amgen, Pfizer; Honoraria: GlaxoSmithKline, Amgen, Novartis, Roche, AstraZeneca, Pfizer; Expert testimony: AstraZeneca, Novartis, GlaxoSmithKline.

As Robson et al. [1] outline, anthracycline regimens have long been a mainstay of adjuvant chemotherapy care in breast cancer. When doxorubicin (Adriamycin; Bedford Laboratories, Bedford, OH) was being moved into practice >30 years ago, we at first feared its side effects, in particular, cardiotoxicity. It soon became apparent, however, that when doxorubicin was given in cumulative doses <450 mg/m², clinical congestive heart failure was relatively rare and other long-term cardiac side effects were not prominent [2, 3]. With the advent of epidoxorubicin (epirubicin), which became widely used in Canada and Europe starting >20 years ago [4] and which had a better antitumor to cardiotoxic ratio [4–9], higher cumulative and more dose-dense and dose-intense regimens of anthracyclines became possible [10–12] in the adjuvant setting. Anthracycline-containing regimens, such as dose-dense doxorubicin and cyclophosphamide plus paclitaxel (AC-T) [13, 14], 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)\textsuperscript{100} [12], FEC plus docetaxel (FEC-D) [11], and the Canadian cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) [10], remain among the most effective in reducing recurrence and preventing death from breast cancer. Indeed, as stated by Robson et al. [1], the 2000 Oxford overview supported a 12% benefit overall from anthracycline-containing regimens [15]. However, when the most dose-dense, dose-intense, and cumulative-dose regimens were compared with the previous standard cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-type regimens, a higher degree of benefit was seen. This can be clearly shown by examining the forest plots from the Oxford overview of anthracycline-containing versus CMF-type regimens [15].

The advent of the taxanes has provided new and effective options for chemotherapy. Once the taxanes were shown, in single-agent, randomized trials, to be similar to and perhaps even slightly better than standard single-agent anthracyclines in the treatment of metastatic disease [16, 17], it seemed clear that combinations of an anthracycline and a taxane might prove to be additionally beneficial. The current Oxford overview (2005–2006) process is carrying out a detailed analysis of the taxane- versus nontaxane-containing regimens, with the regimens classified to address specific questions, including: (a) Does a taxane added to a standard nontaxane regimen provide greater benefit (i.e., AC versus AC-T)? (b) Does a taxane substituted for another drug in a standard chemotherapy regimen provide...
additional benefit?—i.e., docetaxel, doxorubicin, and cyclophosphamide (TAC) versus 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or AC versus doxorubicin and paclitaxel (AT), and other categories. These data will be forthcoming in a full publication. From preliminary examination of these studies, however, it would seem that combinations of the anthracyclines and taxanes together with or separate from other effective drugs may prove to be the most advantageous future strategy in adjuvant therapy. Certainly, a number of regimens, including dose-dense AC-T [14] and the dose dense EC-T regimen explored in the MA.21 trial [18], remain the type of regimen that has proven or may prove to be most effective as adjuvant therapy.

In reviewing the cardiac toxicity of the anthracyclines, as stated by Robson et al. [1], such regimens, in general, have symptomatic congestive failure rates in the range of 0.4% (AC) and 1.1% (Canadian CEF) [10] to 2% (tailored FEC) [19]. Although several studies report rates of asymptomatic left ventricular ejection fraction changes that are higher than this 1%–2% [20, 21], studies such as those of Ganz et al. [22] and Ejertsen et al. [23] suggest that cardiac toxicity is not that great a problem in long-term follow-up. We have similar results from our own MA.5 study (Wendy Parulekar, M.D., NCIC Clinical Trials Group, Queen’s University, Kingston, Ontario, personal communication). Although congestive heart failure is a serious complication and these rates are undoubtedly real, they are not so large as to suggest that effective dose-dense and dose-intensive anthracycline-containing regimens should not be used. Only when, or if, it is very clear that equally or less toxic and equally effective regimens without anthracyclines are available could this decision be made.

The risks for leukemia are, similarly, quite clearly described in the literature as being in the range of 0.27%–1.3% with the National Surgical Adjuvant Breast and Bowel Project AC [24] regimen, 0.6% with the Canadian CEF regimen [24], and about 2% with the tailored-FEC regimen [19]. These rates are undoubtedly related, at least in part, to the anthracyclines contained in them, but may also be connected to the other leukemogens given in these regimens, such as the alkylating agent cyclophosphamide. It seems, however, that the regimens that are more dose dense, are more dose intensive, and contain higher cumulative doses of anthracyclines, particularly epirubicin, perhaps because of its ability to be given at higher doses, do, however, have a stronger relationship with the occurrence of leukemia [24]. Although clearly devastating when this occurs, leukemia remains a relatively low-risk complication that may also occur with nonanthracycline-containing regimens.

It is less clear to me than to Robson et al. [1] that human epidermal growth factor receptor (HER)-2 overexpression or amplification and/or topoisomerase II (TOP2A) overexpression or amplification can clearly pick out patients who will benefit from different types of chemotherapy. This point of view is shared by other senior breast cancer experts [25]. Perhaps, as Slamon et al. [26, 27] suggest, with the right laboratory measurements, this can be done reliably, but other data do not so clearly support the reproducibility of this selection process [28–30]. It seems that measurement issues around HER-2 and particularly TOP2A amplification or amplification and deletion as well as sample size and methodologic problems continue to plague this area. Until these issues are clearly worked out, the ability to pre-select patients who will best respond to anthracyclines remains problematic. Furthermore, because Slamon’s data from the Breast Cancer International Research Group 006 Trial suggest that women with TOP2A amplification in their breast cancer cells can benefit equally well from AC plus docetaxel as from docetaxel, carboplatin, and trastuzumab (TCH), this might suggest that the less expensive and equally effective alternative, AC plus docetaxel, should be given in this subset, rather than TCH. Furthermore, although Slamon’s preliminary data suggest that TCH is equivalent to AC plus docetaxel, these data are still not available in a peer-reviewed accessible fashion and represent the results of only one, albeit large, multicenter trial. In contrast, the Herceptin® Adjuvant Trial, in which 80% of patients received some anthracycline-containing regimen, demonstrated that the addition of trastuzumab to these regimens still provided large additional benefit (>40% reduction in recurrence and 30% reduction in deaths from breast cancer) [32]. Thus, it seems unclear that giving trastuzumab or an anthracycline is necessarily mutually exclusive. There are, in fact, considerable data to support the concept that both should be given to certain patients.

Comparisons between anthracycline- and taxane-containing regimens are few. While the work of Jones et al. [33, 34] suggests that docetaxel plus cyclophosphamide (TC) is superior to AC, most trials have chosen to study regimens that contain an anthracycline and a taxane in comparison with more standard regimens, that is, Lori Goldstein’s study of AT versus AC [35] and the BCIRG trial of TAC versus FAC [36]. Furthermore, comparisons such as that of Jones et al. [33, 34] of TC with AC represent comparisons with a first-generation regimen, with AC and CMF being considered first-generation regimens, AC-T and FEC60 being considered second-generation regimens, and dose-dense ACT, Canadian CEF, and FEC-D being considered third-generation regimens. Thus, it is not clear that the use of a regimen such as TC can totally replace the anthracycline-containing regimens.

It is less clear to me than to Robson et al. [1] that human epidermal growth factor receptor (HER)-2 overexpression or amplification and/or topoisomerase II (TOP2A) overexpression or amplification can clearly pick out patients who will benefit from different types of chemotherapy. This point of view is shared by other senior breast cancer experts [25]. Perhaps, as Slamon et al. [26, 27] suggest, with the right laboratory measurements, this can be done reliably, but other data do not so clearly support the reproducibility of this selection process [28–30]. It seems that measurement issues around HER-2 and particularly TOP2A amplification or amplification and deletion as well as sample size and methodologic problems continue to plague this area. Until these issues are clearly worked out, the ability to pre-select patients who will best respond to anthracyclines remains problematic. Furthermore, because Slamon’s data from the Breast Cancer International Research Group 006 Trial suggest that women with TOP2A amplification in their breast cancer cells can benefit equally well from AC plus docetaxel as from docetaxel, carboplatin, and trastuzumab (TCH), this might suggest that the less expensive and equally effective alternative, AC plus docetaxel, should be given in this subset, rather than TCH. Furthermore, although Slamon’s preliminary data suggest that TCH is equivalent to AC plus docetaxel, these data are still not available in a peer-reviewed accessible fashion and represent the results of only one, albeit large, multicenter trial. In contrast, the Herceptin® Adjuvant Trial, in which 80% of patients received some anthracycline-containing regimen, demonstrated that the addition of trastuzumab to these regimens still provided large additional benefit (>40% reduction in recurrence and 30% reduction in deaths from breast cancer) [32]. Thus, it seems unclear that giving trastuzumab or an anthracycline is necessarily mutually exclusive. There are, in fact, considerable data to support the concept that both should be given to certain patients.

Comparisons between anthracycline- and taxane-containing regimens are few. While the work of Jones et al. [33, 34] suggests that docetaxel plus cyclophosphamide (TC) is superior to AC, most trials have chosen to study regimens that contain an anthracycline and a taxane in comparison with more standard regimens, that is, Lori Goldstein’s study of AT versus AC [35] and the BCIRG trial of TAC versus FAC [36]. Furthermore, comparisons such as that of Jones et al. [33, 34] of TC with AC represent comparisons with a first-generation regimen, with AC and CMF being considered first-generation regimens, AC-T and FEC60 being considered second-generation regimens, and dose-dense ACT, Canadian CEF, and FEC-D being considered third-generation regimens. Thus, it is not clear that the use of a regimen such as TC can totally replace the anthracycline-containing regimens.
In addition, the taxanes in their turn have their own set of toxicities, including some seldom seen with the anthracyclines. Paclitaxel is associated with a 60% incidence of neurosensory toxicity and a 13% incidence of neuromotor toxicity (7.2% and 4.1% for grades 3 and 4, respectively), some of which persists beyond 1 year and can be quite debilitating. Docetaxel given at the suggested adjuvant dose of 100 mg/m² produces a 64% incidence of neurosensory toxicity and a 28% incidence of neurotoxicity, as well as a febrile neutropenia rate of ~15%, and often requires administration with colony-stimulating factors [16, 17, 37].

Furthermore, the platinum-containing regimens such as TCH have had few comparisons with more established therapies and their relative efficacy is therefore less robustly anchored than other more traditional regimens. Moreover, long-term follow-up of platinum-containing regimens in germ cell tumors has demonstrated a significantly greater incidence of cardiovascular events, including myocardial infarction, and so the long-term cardiac safety of regimens such as TCH remains to be documented. There have also been reports of secondary leukemias as part of long-term toxicity after both cisplatin and carboplatin [38–40].

In summary, anthracyclines in early-stage breast cancer: Is it the end of an era? Eras come, go, and overlap. Much from the past is recreated in the future. I recently attended a Toronto Symphony Orchestra concert where works by Ricard Strauss and Bela Bartok were played in the same concert. Our always delightful and informative Toronto Symphony conductor, Peter Oundjian, pointed out that these seemingly different composers, one regarded as being from the romantic era and one definitely modern, overlapped each other virtually completely in their life spans and composing years. The anthracyclines and taxanes will undoubtedly prove to be similar. I believe that they will both be used in the future, that one will not replace the other, and that their value and, for all their toxicities, their important clinical roles will both persist in the adjuvant therapy of breast cancer for some time to come.

REFERENCES

18 Bergh J, Wiklund T, Erikstein B et al. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: A randomised


29 Bartlett JMS, Munro A, Cameron DA et al. Type 1 receptor tyrosine kinase profiles identify patients with enhanced benefit from anthracyclines in the BR9601 adjuvant breast cancer chemotherapy trial. J Clin Oncol 2008;26:5027–5035.