REVIEW

Adjuvant chemotherapy in breast cancer: To use or not to use, the anthracyclines

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Abstract

Breast cancer continues to be one of the leading causes of cancer mortality in the world. The treatment generally involves multiple modalities including surgery, radiation and/or chemotherapy. Anthracyclines, one of the first chemotherapeutic agents introduced in the 1960s, has been the backbone for the last 30 years and has been used extensively so far. However, the cardiac toxicity and the concern for secondary hematological malignancy has always been a challenge. A better understanding of the tumor biology, role of Her2 expression and the discovery of trastuzumab and other anti-Her 2 agents along with other effective novel therapeutic options, have revolutionized the treatment for breast cancer. The role of anthracyclines has come under close scrutiny, especially in the adjuvant setting for patients with early stage breast cancer and those with low or intermediate risk of disease recurrence. Recent studies have highlighted such a shift in the use of anthracyclines in both the academic and community clinical practice. However, in patients with a high risk of relapse, anthracyclines still hold promise. Ongoing clinical trials are underway to further define the role of anthracyclines in such a patient population. This review highlights the development, clinical utility, limitations and potential future use of anthracyclines in the adjuvant setting for patients with breast cancer. We consulted PubMed, Scopus, MEDLINE, ASCO annual symposium abstracts, and http://clinicaltrials.gov/ for the purpose of this review.

Key words: Breast cancer; Adjuvant; Neoadjuvant; Chemotherapy; Anthracyclines

Core tip: A better understanding of the tumor biology along with other effective novel therapeutic options, have revolutionized the treatment for breast cancer. The role of anthracyclines has come under close scrutiny, especially in the adjuvant setting for patients with early stage breast cancer and those with low or intermediate risk of disease recurrence, as per the recent studies. However, in patients with a high risk of relapse, anthracyclines still hold promise. Ongoing clinical trials are underway to further define the role of anthracyclines in such a patient population.

INTRODUCTION

Approximately 230000 new cases of female breast cancer are diagnosed annually in the United States[1]. The probability of developing invasive breast cancer in one's lifetime is one in eight[2]. Breast cancer is a heterogeneous disease with common aspects to treatment including surgery, chemotherapy and radiation therapy. Systemic (neo)adjuvant chemotherapy, cytotoxic treatment before

or following primary surgery, is responsible in part for the reduction in cause-specific mortality from breast cancer[3]. In the 1960s and early 1970s the anthracyclines emerged as a novel therapeutic agent against metastatic breast cancer and by the late 1970s the very first adjuvant trials with these agents were reported[4-8]. By the 1980s, doxorubicin-based combination regimens established themselves as a primary class of chemotherapy regimens used in the treatment of early and advanced stage breast cancer[5]. The introduction of new and effective therapeutic agents in combination with some of the irreversible and/or long term adverse events of the anthracycline group of drugs has now questioned their use in the (neo)adjuvant setting[9].

PATIENT SELECTION/INDICATIONS FOR TREATMENT

Multiple components determine the necessity for patients requiring adjuvant chemotherapy. These include but are not limited to the tumor size, molecular subtype, histology and its grade. The axillary and regional lymph node status and the tumor hormone receptor expression are also important considerations. Finally, the patient's age, concomitant co-morbidities and their performance status play a significant role in determining the benefit of (neo)adjuvant chemotherapy. Other histologies require more information regarding size and nodal status to delineate the role of chemotherapy. Tumor size in the setting of regional disease is an independent prognostic factor with five-year overall survival (OS) for tumors $\leq$ 2 cm, 2.1 to 5 cm and $\geq$ 5 cm being 95, 82 and 63 percent, respectively[10]. Nodal status also plays a role with any nodal involvement lowering the survival rate at five years[11].

ESTIMATING THE BENEFIT/RISK RATIO

Despite all of the components above, selection of patients for adjuvant chemotherapy requires an individualized approach that has been enhanced by the use of benefit *vs* risk calculators. One of the most widely studied and validated tool is Adjuvant! Online[12]. Adjuvant! Online is a web based program that aims to help health care professionals discuss the risk and benefits of getting additional therapy including chemotherapy, hormone therapy, or both after surgery for early stage cancer[13]. The calculator uses resources such as Surveillance, Epidemiology, and End Results (SEER) database and data on adjuvant therapy from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), as well as data from several pivotal adjuvant clinical trials. It helps make approximations of the risk of a negative outcome (cancer related mortality or relapse) without systemic adjuvant therapy and calculates the estimates of the reduction of these risks afforded by therapy. These estimates are based on information entered about individual patients and their tumors (including patient age,

tumor size, nodal involvement, histologic grade, *etc*.)[13]. In addition to the above risk calculator, the last decade has also witnessed the emergence of genomic profiling of the primary tumor with tests like Oncotype DX®, Mammaprint® and PAM50, which allows for better risk prognostication and in some of them a predictive benefit of adjuvant therapies[14-16]. The review of these tools are beyond the scope of this article but needless to say, they have allowed to better define the population of patients that should consider adjuvant chemotherapy. This substantially helps both providers and patients to better assess the worthiness of the potential benefits of chemotherapy as compared to their known probable short and long term side effects.

DATA SUPPORTING ADJUVANT THERAPY WITH ANTHRACYCLINES

The EBCTCG meets every five years to review data from global breast cancer trials. The 2011 EBCTCG meta-analysis included an analysis of the utility of adjuvant chemotherapy. One analysis compared no treatment to the combination of cyclophosphamide, methotrexate, and 5-fluoruracil (CMF) compared to an anthracycline containing regimen. Compared to no treatment, the use of CMF in 5253 women resulted in a significant improvement in the risk of recurrence at 10 years [risk ratio (RR), 0.70, 95%CI: 0.63-0.77], which translated into an absolute gain of 10.2 percent. There was also a significant reduction in breast cancer mortality (RR, 0.76, 95%CI: 0.68-0.84), validating a complete benefit of 6.2 percent. Lastly, there was a significant reduction in overall mortality (RR, 0.84, 95%CI: 0.76-0.93), thereby demonstrating an absolute gain of 4.7 percent[17]. Comparatively the use of an anthracycline containing regimen compared to no treatment in 8575 women established a significant improvement in the risk of recurrence at 10 years (RR, 0.73, 95%CI: 0.68-0.79), which resulted in a total gain of 8.0 percent. There was also a significant reduction in breast cancer mortality (RR, 0.79, 95%CI: 0.72-0.85), ensuing an absolute improvement of 6.5 percent and a significant reduction in overall mortality (RR, 0.84, 95%CI: 0.78-0.91), confirming an absolute benefit of 5.0 percent[17].

The 2011 EBCTCG meta-analysis also compared the dosing regimens of anthracyclines *vs* CMF. The standard dose of anthracyclines was defined as a cumulative dose of doxorubicin of 240 mg/m^2 *vs* the high dose defined as doxorubicin > 240 mg/m^2 or epirubicin > 360 mg/m^2[17]. The 10 year results of this analysis in 5122 women showed that standard dosing of anthracyclines was equivalent to CMF with no improvement in the risk of recurrence, breast cancer mortality or overall mortality[17]. An analysis of 9527 women receiving either higher cumulative doses of anthracyclines or CMF were compared at 10 years with a reduction in the risk of recurrence (RR, 0.89, 95%CI: 0.82-0.96), which translated into an absolute gain of 2.6 percent. There was also a reduction in breast cancer mortality (RR, 0.80, 95%CI: 0.72-0.88) with

an absolute gain of 4.1 percent and a reduction in overall mortality (RR, 0.84, 95%CI: 0.76-0.92) with an absolute gain of 3.9 percent[17]. These results suggest standard dosing anthracycline regimens are equal to CMF but slightly inferior to regimens including higher cumulative doses of anthracyclines, *i.e.*, 6 cycles of an anthracycline-based regimen being better than 4 cycles. No single regimen has been defined as the absolute gold standard treatment but based on well conducted prospective trials and meta-analyses conducted by the EBCTCG, anthracycline-based regimens have been recommended for more than 2 decades[17-19].

The 2011 EBCTCG meta-analysis also included taxanes such as docetaxel and paclitaxel in its analysis of adjuvant therapy. Incorporation of taxanes into an anthracycline containing regimen resulted at 8 years in the reduction of the risk of recurrence, risk of breast cancer mortality, and overall mortality. This benefit was present independent of age, nodal status, tumor size, tumor grade or estrogen receptor (ER) status[17].

Studies have also examined the dose intensity of the adjuvant regimens. A meta-analysis of dose dense therapy *vs* standard therapy in 10 trials of over 11000 women reported an improvement in disease free survival (DFS) with dose dense therapy in women with estrogen receptor (ER)-negative disease (HR, 0.71, 95%CI: 0.56-0.98), but not in women with ER-positive disease (HR, 0.92, 95%CI: 0.75-1.12)[18]. Another analysis of three randomized trials involving 6644 women with node positive breast cancer and variable hormone receptor status demonstrated that women with ER-negative breast cancer had a larger reduction in the risk of recurrence compared to women with ER-positive breast cancer at 5 years, (55% *vs* 26%, respectively). There was also a higher absolute improvement in DFS (23% *vs* 7%) and higher absolute improvement in OS (17% *vs* 4 %)[19].

PROBLEMS WITH THE ANTHRACYCLINES

Cardiotoxicity and secondary MDS/AML are two significant long-term toxicities of anthracycline use. Anthracycline cardiotoxicity is believed to be derived from damage to the myocardium from free reactive oxygen radicals, direct DNA damage, interference with DNA repair, and induction of immune reactions leading to cardiomyocyte apoptosis[20-22]. This damage leads to a decrease in the left ventricular ejection function, and although could be reversed with good medical management, in many cases could be an irreversible long term problem. The risk of MDS/AML remains rare at 0.5%-1% but it carries a high mortality rate due to its association with poor cytogenetics and refractory nature to standard treatment[23,24].

ANTHRACYCLINE TOXICITY

Cardiotoxicity

Anthracyclines are associated with cardiovascular tox-

icities including abnormal electrocardiogram (sinus tachycardia and transient arrhythmias), cardiomyopathy, acute and late-onset congestive heart failure (CHF), myocarditis, pericarditis and myocardial infarction[25,26]. The incidence of cardiomyopathy and heart failure secondary to anthracyclines has been shown to be dose dependent and generally occurs at higher doses than the dosages administered in the adjuvant setting. However, some of the other acute cardiac events are often not dose related and could occur as soon as after the first dose[27,28]. The risk of chronic cardiomyopathy and CHF increases substantially at cumulative doses of doxorubicin greater than 400-500 mg/m^2[28] and epirubicin greater than 800-1000 mg/m^2[28]. It is estimated that the overall risk of cardiac toxicity using standard dose anthracyclines in the general population is approximately 1%-3%, however, such risk varies greatly depending on the population of women studied. Older studies that included patients who received higher cumulative doses of anthracyclines report a higher incidence rate whereas newer clinical trials have an insufficient follow up time to accurately assess the long-term incidence of CHF[29]. An older but long-term prospective trial of 120 patients with advanced breast cancer showed that those patients receiving high cumulative doses of epirubicin (850-1000 mg/m^2) had the highest risk of CHF with 11% at 1 year, 14% at 2 years and 20% at 5 years[30]. Also of note, those patients receiving long term treatment with an angiotensin converting enzyme inhibitor had a significant and long term recovery in cardiac function[30].

Certain populations including older women are at increased risk with a retrospective study of 12500 women with invasive breast cancer showing a 5-year cumulative incidence of CHF of 6 percent among women aged 65 to 74 and 11 percent among women aged ≥ 75 years[31]. This was in stark contrast to younger women with a cumulative incidence of 1-2 percent. With the addition of biologic agents including trastuzumab there is a concern for additive cardiotoxicity. In women treated with an anthracycline plus trastuzumab, there was a cumulative CHF incidence of 20 percent which represented an increased risk compared to patients who did not receive an anthracycline or trastuzumab [hazzd ratio (HR), 7.19, 95%CI: 5-10.4][31]. The risk was also increased among patients treated with trastuzumab without an anthracycline (HR, 4.12, 95%CI: 1.11-1.76)[31]. Of note in this study only 11.2 percent of women over the age of 65 received an anthracycline based therapy[31]. Another study supporting the increased risk in older women reviewed 43338 patients with breast cancer treated with chemotherapy through the SEER database[32]. The authors concluded women aged 66 to 70 years who received adjuvant anthracyclines had significantly higher rates of CHF, 38.4% of the anthracycline-treated group compared with 32.5% of the patients who received non-anthracycline chemotherapy and 29% in the no-chemotherapy group[32]. The difference in rates of CHF continued to increase through more than 10 years of follow-up[32].

There has also been data that have not supported long term cardiac adverse effect of adjuvant anthracycline therapy. Patients treated on the Southwest Oncology Group (SWOG) protocol S8897 were randomly assigned to adjuvant chemotherapy with or without the anthracycline doxorubicin. A retrospective study evaluated the left ventricular ejection fraction (LVEF) at 5 to 8 years and 10 to 13 years after treatment randomization[33]. A total of 93 breast cancer survivors from a potential sample of 1176 patients completed the longitudinal assessment of LVEF[33]. In the longitudinal analysis, there was no significant deterioration in LVEF concluding that the exposure to doxorubicin did not increase the likelihood of adverse cardiac effects[33]. However, as noted the studied population was very small.

Risk of MDS and AML

Another well-known serious and concerning adverse event from the use of anthracycline is the development of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Multiple cytotoxic agents have been implicated including those more commonly used in breast cancer including cyclophosphamide, doxorubicin, daunorubicin and epirubicin. The incidence among breast cancer patients varies among different retrospective studies. In a review of 6 adjuvant National Surgical Adjuvant Breast and Bowel Project (NASBP) breast cancer trials (B-15, B-16, B-18, B-22, B-23, and B-25) the incidence of AML/MDS was sharply elevated in patients receiving standard dose doxorubicin (60 mg/m^2 × 4) plus higher doses of the alkylating agent cyclophosphamide. In this study, those regimens with two or four cycles of cyclophosphamide at 2400 mg/m^2 (with granulocyte colony-stimulating factor (G-CSF) support) had a cumulative incidence of AML/MDS at 5 years of 1.01% (95%CI: 0.63% to 1.62%), compared with 0.21% (95%CI: 0.11% to 0.41%), for patients receiving 4 cycles of standard doxorubicin/cyclophosphamide (AC) chemotherapy[34]. Also patients who additionally received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR, 2.38, *P* = 0.006)[34]. This study also suggested that the use of G-CSF may be an independent factor associated with increased risk of MDS/AML but this may be secondary to the use of higher doses of leukemogenic chemotherapy agents.

Therapy related myeloid neoplasms (t-MN) have on average a latency period of five to seven years[35]. Praga and colleagues reviewed the incidence of AML/MDS in 19 randomized trials involving 7110 patients who had received adjuvant epirubicin and cyclophosphamide[24]. Patients with administered cumulative doses of both epirubicin and cyclophosphamide in standard regimens (≤ 720 mg/m^2 and ≤ 6300 mg/m^2, respectively) had an 8-year cumulative probability of developing AML/MDS of 0.37% (95%CI: 0.13% to 0.61%) compared with 4.97% (95%CI: 2.06% to 7.87%) for patients administered higher cumulative doses of both epirubicin and cyclophosphamide[24]. Patients most commonly present with persistent hematologic abnormalities such as macrocytic anemia or pancytopenia in peripheral blood and bone marrow evaluation reveals changes consistent with MDS or AML. Cytogenetics plays an important role in the prognosis of AML. In patients with t-MN there is a higher incidence of unfavorable cytogenetics compared to de novo AML (46.2% *vs* 20.4%)[36]. Unfavorable genetics affect OS even more in treatment related AML compared to de novo AML (10 mo *vs* 15 mo, *P* < 0.001)[36].

ANTHRACYCLINE *VS* NON-ANTHRACYCLINE ADJUVANT REGIMENS

The MA.5 trial directly compared an anthracycline to a non anthracycline regimen[37]. The trial enrolled 710 pre and peri-menopausal women with node positive breast cancer. Patients were randomly assigned to receive cyclophosphamide, epirubicin, and fluorouracil (CEF) or cyclophosphamide, methotrexate, and fluorouracil (CMF). The 10-year relapse free survival was 52% for patients who received CEF compared with 45% for CMF patients (HR for CMF *vs* CEF = 1.31; stratified log-rank, *P* = 0.007). The 10-year OS for patients who received CEF and CMF are 62% and 58%, respectively (HR for CMF *vs* CEF = 1.18; stratified log-rank, *P* = 0.085) These results support the previous 5 year follow up data with CEF being superior to CMF[38]. This trial was not powered for comparison of treatment regimens in subgroups based on nodes or hormone receptor status, however, the HRs favored CEF in patients with one to three nodes and four or more nodes[37].

The National Surgical Adjuvant Breast and Bowel Project (NASBP) 23 trial was another direct comparison of an anthracycline to a non-anthracycline containing regimen[39]. 2008 patients were randomly assigned to CMF or AC with or without tamoxifen. In contrasting results a comparison between all CMF and all AC treated patients demonstrated no significant differences in relapse free survival (RFS) (87% at 5 years in both groups, *P* = 0.9), event free survival (EFS) (83% and 82%, *P* = 0.6), or OS (89% and 90%, *P* = 0.4)[39].

As noted above, the CMF regimen has been a well-established non-anthracycline-containing regimen but its lack of superiority and longer duration of therapy led to its relative abandonment by the oncologic community in the 1990s. However, it still has an important role for patients who are not candidates for anthracycline and/or taxane-based regimens. Capecitabine, an oral prodrug that is converted to 5-fluorouracil, and approved for the treatment of metastatic breast cancer, has been evaluated in the adjuvant setting as a possibly more convenient and less toxic chemotherapy for older women. The Cancer and Leukemia Group B study CALGB 49907 was a randomly assigned trial comparing standard chemotherapy (AC or CMF per patient/provider's choice) *vs* oral chemotherapy with capecitabine in patients age 65 years or older with early-stage breast cancer[40]. Unfortunately the

study demonstrated that capecitabine therapy was highly likely to be inferior to standard chemotherapy and patients who were randomly assigned to capecitabine were twice as likely to have a relapse and almost twice as likely to die as compared to patients who were randomly assigned to standard chemotherapy ($P = 0.02$).

Docetaxel plus cyclophosphamide has become one of the most popular adjuvant regimens of the last decade. This is based on the long term results of the US Oncology adjuvant trial 9735, which enrolled 1016 patients, age 18 to 75 years, with stage Ⅰ-Ⅲ breast cancer (irrespective of nodal, hormonal or HER2 status) and reported a statistically significant superiority of docetaxel-cyclophosphamide (TC) over doxorubicin-cyclophosphamide (AC)[41]. At a median of 7 years follow-up, there was a statistical improvement in disease-free survival between TC and AC (81% TC *vs* 75% AC; $P = 0.033$; HR, 0.74; 95%CI: 0.56-0.98) as well as an OS (87% TC *vs* 82% AC; $P = 0.032$; HR, 0.69; 95%CI: 0.50-0.97). Benefit was observed irrespectively of hormone-receptor status or HER-2 status. TC was noted to be superior in all age groups with the caveat that more febrile neutropenia (FN) was observed in the older population defined by a cutoff of 65 years (for TC, the rate of FN was 8% for the older population and 4% for younger patients compared with 4% in older and 2% in younger patients who received AC). Notably, the use of prophylactic granulocyte colony-stimulating factor to stimulate neutrophil production was not utilized in this study. Of concern is that 4 late deaths were observed in patients without relapse and all occurred in the AC group: a young woman died of cardiomyopathy and CHF, two older women died of complications related to myelodysplasia and myelofibrosis respectively, and 1 other patient died of acute leukemia 10 years after AC. The US Oncology group is now involved in a new study (USO 06090 phase Ⅲ trial), that will further evaluate the need for anthracyclines by comparing six cycles of TC (plus/minus bevacizumab) against six cycles of TAC (docetaxel/doxorubicin/cyclophosphamide) for 3900 patients with HER2-negative resected breast cancer. We are eagerly awaiting the results of this trial.

The CALGB 40101 trial enrolled 3171 women with early stage breast cancer who were randomized in a 2 × 2 factorial design to AC once every 3 wk for four (12 wk) or six (18 wk) cycles *vs* paclitaxel (T) weekly for 12 or 18 wk (3 wk of T was considered one cycle)[42]. So far, what has been reported is the comparison of 4 *vs* 6 cycles of therapy. The 4-year RFS was 90.9% for patients randomly assigned to six cycles of therapy and 91.8% for patients randomly assigned to four cycles. The 4-year OS for patients randomly assigned to six cycles of therapy was 95.3% as compared to 96.3% for patients randomly assigned to four cycles of therapy. The conclusion of the study established that six cycles of therapy was not superior to four cycles for either RFS or OS after adjusting for the effects of tumor size, number of positive nodes, hormone receptor status, and menopausal status. There were a total of 28 patients in the AC arms that developed grade 3 or 4 (G3-G4) left ventricular systolic dysfunction (LVSD) and 1 G5. There was also 1 patient in the AC x 4 cycles that died of acute myocardial infarction. This is in stark contrast with no cases of LVSD in the T × 4 cycles arm and only 3 G3-4 LVSD in the T × 6 cycles arm. Six patients were diagnosed with AML/MDS between 11 and 28 mo after initiation of treatment; 5 in the AC × 6 arm and 1 in the AC × 4 arm. Patients were between 44 and 62 years of age at the time of study enrollment. No cases of AML/MDS occurred in patients treated with T. The study's data safety monitoring board has not yet released data for the efficacy comparison of AC *vs* T, but we presume that it is likely that no major differences will be noted as this trial enrolled all of these patients several years ago, between May 2002 and February 2008.

EARLY STAGE HER2 POSITIVE TUMORS

It has been hypothesized that a specific population of patients who may benefit from the use of anthracycline is that of patients with HER2 positive tumors[43]. The National Surgical - Breast and Bowel Project 31 (NSABP B-31) trial included women with HER2 positive, node positive breast cancer. Patients were assigned to treatment with doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with or without trastuzumab (H) therapy. In conjunction with this trial was the North Central Cancer Treatment Group (NCCTG) intergroup trial N9831 which enrolled women with HER2 positive node positive or high-risk node negative breast cancer. The women were treated with AC and T followed by no treatment, AC and T followed by sequential H or AC followed by concurrent T and H. From these two trials at a median follow up of 3.9 years, chemotherapy plus adjuvant trastuzumab compared to treatment without trastuzumab resulted in significantly superior DFS (86% *vs* 74%, HR 0.52) and OS (93% *vs* 86%, HR 0.61)[44].

Anthracycline *vs* non-anthracycline based therapy was compared during the Breast Cancer International Research Group 006 (BCIRG-006) trial of 3222 women with HER2-positive, node-positive or high-risk node negative disease. Patients were randomly assigned to adjuvant treatment with AC-T (doxorubicin and cyclophosphamide followed by docetaxel), ACTH (AC followed by T plus trastuzumab) or TCH (docetaxel, carboplatin and trastuzumab)[45]. With a median follow up of 65 mo patients treated with an anthracycline (ACTH) compared to treatment without an anthracycline (TCH) demonstrated a trend towards an improvement in DFS, rates at 5 years were 84% and 81%, respectively. Estimated rates of OS were 92%, and 91%, respectively. These rates for DFS and OS did not reach statistical significance but the study was actually not powered or designed to compare equivalence between the two trastuzumab-containing groups (ACTH *vs* TCH)[45]. Conversely, patients receiving ACTH had significantly higher rates of adverse events including CHF, neuropathy and severe neutropenia[45].

The incidence of symptomatic congestive heart failure in the two trastuzumab-containing regimens was higher in the group receiving ACTH than in the TCH group (2.0% *vs* 0.4%, *P* < 0.001)[45]. In addition, a significant difference in sustained, subclinical loss of mean LVEF (defined as > 10% relative loss) was observed in the group receiving ACTH, as compared with the TCH group (18.6% *vs* 9.4%, *P* < 0.001)[45]. Neuropathy was significantly worse in patients receiving ACTH (49.7% *vs* 36%, *P* < 0.001) as was neutropenia (71.5% *vs* 65.9%, *P* = 0.01)[45].

The evaluation of whether HER-2 positivity is associated to anthracycline sensitivity has been attempted in a number of adjuvant trials. A pooled analysis of eight of such trials revealed that, for those women randomized to anthracycline *vs* non-anthracycline regimens, the DFS and OS HRs for women with HER-2 positive tumors were markedly superior, at 0.71 (95%CI: 0.62-0.85) and 0.73 (95%CI: 0.62-0.85), respectively[46]. However, such differential benefit seems to be lost when trastuzumab is added to the adjuvant regimen[45]. Additionally, a higher incidence of cardiotoxicity has been noted when trastuzumab is used with regimens containing an anthracycline[47].

In evaluating HER2 positivity and anthracycline sensitivity, topoisomerase 2-alpha (TOP2A) has been evaluated as well to see whether TOP2A gene alterations could predict incremental responsiveness to anthracyclines in some breast cancers. Some studies have supported the concept that TOP2A co-amplification is the clinically useful target of the anthracyclines and its co-amplification in tumors could be used as a predictive marker of responsiveness to anthracyclines[48]. A 2011 meta-analysis evaluated the relationship of HER2 and TOP2A status in patients who received either a non-anthracycline based regimen (CMF) *vs* anthracycline based regimens in the adjuvant setting of early stage breast cancer. Tumors from 3452 patients were analyzed for HER2 status (amplified *vs* non-amplified), and from 3102 patients for TOP2A (normal, amplified, or deleted) by fluorescent *in-situ* hybridization (FISH). Although there was a significant improvement in event-free survival (but not OS), for patients with HER2 overexpression treated with anthracyclines compared to CMF and for both outcomes in patients with TOP2A alterations (*vs* TOP2A normal), treated with anthracyclines, the authors concluded that there was not enough evidence to restrict the use of anthracyclines only in patients with HER2-amplified or TOP2A-altered tumors. The main reasons for this conclusion were that women with non-HER2 amplified and non-TOP2A altered tumors also derived benefits when treated with anthracyclines, and because problems exist with the reproducibility of TOP2A gene status assessment by FISH[49]. Jones and colleagues completed a recent phase 2, single group study of adjuvant therapy with docetaxel, cyclophosphamide, and trastuzumab in *HER2*-amplified patients with early breast cancer and a low risk of recurrence (node negative or 1-3 positive nodes)[50]. They enrolled 493 patients with HER2 positive tumors, that were TOP2A gene positive or negative, to receive four 21-d cycles of docetaxel (75

mg/m^2) and cyclophosphamide (600 mg/m^2), plus intravenous trastuzumab (4 mg/kg [loading dose] on day 1 and 2 mg/kg on days 1, 8, and 15 during chemotherapy, followed by trastuzumab 6 mg/kg every three weeks for the rest of 1 year). Follow up at 2 years revealed DFS was 97.8% (95%CI: 94.2-99.2) in the 190 TOP2A-amplified patients and 97.9% (94.9-99.1) in the 248 patients without amplified TOP2A and OS was higher than 98% in both groups. Investigators found a low occurrence of cardiotoxicity. The investigators concluded that a short course of adjuvant chemotherapy with docetaxel and cyclophosphamide plus trastuzumab might be an option in patients with lower risk HER2-amplified early breast cancer irrespective of TOP2A status as an alternative to an anthracycline containing regimen.

Targeted therapy

New agents are constantly being developed against known and novel targets. Currently such novel agents, such as VEGF (vascular endothelial growth factor), PARP (poly ADP ribose polymerase), mTOR (*mammalian target of rapamycin)* and HDAC (histone deacetylase) inhibitors, are being studied in the neo-adjuvant, adjuvant and metastatic setting, along with anthracycline and non-anthracycline containing regimens[51]. These clinical trials will provide information on whether they can improve the outcome of patients with breast cancer and their interaction with the different standard chemotherapy agents. The targeted agent most studied has been bevacizumab, but a discussion of its potential benefits or of any of the other agents are beyond the scope of this review.

DISCUSSION

In accordance to all the data reviewed in this manuscript, the indiscriminate use of anthracyclines in the adjuvant setting has become very controversial. Humans are creatures of habit and change is often uncomfortable. Physicians are no exception and it is well known that changes in patterns of practice can take a long time. The use of (neo)adjuvant chemotherapy has certainly contributed to the decline in disease relapse and improvement in survival as noted in the last 30 years in patients with all types of early stage breast cancer. The anthracyclines have been the backbone of most adjuvant chemotherapy regimens since the 1980s and it certainly has served us well. However, emerging evidence demonstrates that anthracyclines may not be critical to the adjuvant treatment of breast cancer and such a change is being observed in practice overall. Additionally, the current evidence also suggests that the specific benefits of anthracyclines are very difficult to substantiate for HER2 positive tumors in the era of the great equalizer trastuzumab and other targeted anti-HER2 agents.

Investigators at the University of California, San Francisco Breast Cancer Center examined the charts of 1116 patients treated for breast cancer between 2000 and 2010[52]. They examined the use of anthracycline contain-

ing chemotherapy regimens against the non-anthracycline containing. From 2000-2005, 95% of chemotherapy regimens included an anthracycline compared to 65% from 2005-2010. Another study from Giordano *et al*[53], looking at claims from 4458 Medicare beneficiaries and 30422 privately-insured population (Marketscan), demonstrated that a sharp increase in the use of taxane-based chemotherapy and a decline in anthracycline-based chemotherapy had occurred during the study period (1998-2009). Such change seemed to appear in late 2005 and the crossover occurred in late 2007. By the end of the study period, 51% of patients in the Medicare cohort received taxane-based and only 32% received anthracycline-based chemotherapy. A similar pattern of care was noted in the privately insured population. An additional important observation was seen among trastuzumab recipients, in the private market, use of docetaxel increased from 34.4% of women in 2005 to 61.7% of women in 2008, and for patients who did not receive trastuzumab, the use of docetaxel changed from 42.6% in 2005 to 59.4% in 2008. Similar findings were also noted in the Medicare cohort. In the trastuzumab recipients, the rate of docetaxel increased from 62.5% of patients in 2005 to 74.5% of patients in 2008, and in patients who did not receive trastuzumab, docetaxel increased from 44.2% in 2005, to 88.8% in 2008. These changes likely reflect the increasing popularity of the docetaxel/cyclophosphamide (TC) regimen for patients with HER2 negative disease and of the docetaxel/carboplatin/trastuzumab (TCH) regimen for patients with HER2 positive disease. Also of relevance is that, patients who underwent the 21-gene recurrence score testing Oncotype DX® were more likely to receive a taxane-based chemotherapy.

Based on the emerging data it seems that patients felt to be at lower or intermediate risk of relapse are being treated with non-anthracycline regimens in the adjuvant setting. But is there a population that should still receive an anthracycline based-regimen? We personally believe that the anthracyclines still have an important role in the (neo)adjuvant care of patients with early stage breast cancer. Anthracyclines plus taxanes are important components of what is called today "third generation regimens"[13]. These include regimens such as 3 cycles of CEF followed by 3 cycles of docetaxel (CEF-D) as developed in the PACS 01 trial[54]; 4 cycles of AC followed by paclitaxel or docetaxel as used in the CALGB 9741 and ECOG 1199 clinical trials[55,56], 6 cycles of doxorubicin, cyclophosphamide and docetaxel (TAC) as in the BCIRG 001 trial[57] and the trastuzumab containing regimens from the NCCTG 9831, NSABP B-31 and BCIRG 006 studies previously discussed[44,45]. These regimens have demonstrated in large prospective randomized trials to yield the best relative risk reduction in breast cancer relapse, especially for those patients with high recurrence risk (large primary tumors, presence of nodal metastasis, estrogen receptor negative tumors, HER2 positive tumors), and almost all of them were built with a backbone of anthracyclines. Until new trials, such as USO 06090

and/or others comparing the use of anthracycline *vs* non-anthracycline regimens, are able to show either the lack of superiority of the anthracycline regimen or the non-inferiority of the non-anthracycline regimen, there is still a role for its use in high-risk patients. The only high risk sub-group that could certainly obviate the use of an anthracycline is the population with HER2 positive disease. However, patients should be made aware of the small differences in 5-year DFS between the AC-T and trastuzumab *vs* the TCH regimen (84% *vs* 81% respectively), and that although this was not "statistically different", as it wasn't the difference in 5-year OS (92% *vs* 91% respectively), the study was not powered to detect equivalence between these 2 regimens. That 3% DFS difference may be considered clinically significant by the patient and her provider.

CONCLUSION

The current role of adjuvant anthracycline-based chemotherapy in early-stage breast cancer is very much in question. It is very reasonable to substitute such for well-established non-anthracycline regimens for patients considered at lower or intermediate risk of disease recurrence. However, for those at high risk we need more comparative studies to totally abandon a family of drugs that contributed to the decline in breast cancer relapse and improvement in related survival over the last 3 decades. Most importantly, the increasing prospectively conducted research using genomic profiling, will hopefully allow for better risk prognostication and predictive benefit of adjuvant therapies and lead us to spare many from the adverse events of any type of chemotherapy.

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