Long-term toxic effects of adjuvant chemotherapy in breast cancer

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Breast cancer is the most common malignant tumor affecting women. Adjuvant systemic therapies have been shown to have a significant impact on reducing the risk for breast cancer recurrence and overall mortality. Chemotherapy remains an important and frequently used treatment option in the adjuvant setting, and the associated short-term adverse events are very well described. However, there is insufficient information regarding the long-term sequelae of most chemotherapeutic agents. In this review, we describe different potential long-term adverse events associated with adjuvant chemotherapy in breast cancer, with a particular focus on long-term cardiac toxicity, secondary leukemia, cognitive function, and neurotoxicity. In addition, we discuss the effect of adjuvant chemotherapy on fertility and sexual function of young breast cancer patients. These adverse events are frequently overshadowed by the well-demonstrated clinical efficacy and/or reassuring short-term safety profiles of the different chemotherapy regimens commonly used today. We believe that a proper understanding and appreciation of these adverse events will enable us to refine our strategies for managing breast cancer. The fact that adjuvant chemotherapy is often given to patients who might not really need it urges us to consider the whole spectrum of chemotherapy risks versus benefits to maximize benefit without compromising quality of life.

Key words: adjuvant breast cancer, cardiac toxicity, chemotherapy, cognitive function, fertility, long-term toxicity

Introduction

Chemotherapy in the adjuvant setting has contributed to significant progress in the management of breast cancer. During the past few decades, we have witnessed a paradigm shift, moving from classic CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) to anthracycline-based regimens, to the subsequent incorporation of taxanes, administration of dose-dense regimens, and, most recently, the use of biological agents [1]. Both earlier diagnosis of the disease and novel chemotherapy strategies have resulted in a considerable improvement in breast cancer survival [2, 3]. However, given the curative intent of adjuvant therapies, it is vital to address issues related to long-term toxic effects that could affect the overall quality of patient survival.

The primary objectives of chemotherapy adjuvant trials have been predominantly focused on breast cancer outcome and short-term patient safety. Little attention has been given to the long-term side-effects of these drugs. This is of paramount importance as long-term effects could considerably compromise patients’ quality of life (QoL). Also, a better understanding of the whole spectrum of chemotherapy adverse events—both short and long term—would enable us to refine our use of such therapy, in terms of both scheduling and individual patients’ risks and preferences.

In this review, we focus on the long-term toxic effects associated with chemotherapy regimens commonly given in the adjuvant setting. We shed light on different adverse events, discussing their magnitude, clinical implications, and possible management strategies. The long-term toxic effects related to endocrine and targeted agents are not covered in this review.

Cardiac toxicity

Anthracycline-based regimens with doxorubicin or epirubicin have been widely used in the adjuvant treatment of breast cancer since the 1980s. It is very well described that these agents carry a significant risk for cardiac toxicity, which is exponentially dose dependent [4]. The incidence of congestive heart failure (CHF) reaches 5% for doxorubicin and epirubicin, with cumulative doses of 400 and 920 mg/m², respectively [5, 6]. The main risk factors include old age, hypertension, precocious coronary artery disease, and previous mediastinal radiotherapy [4, 5, 7].

Anthracyclines are believed to cause immediate damage to the myocardial cells by generating free radicals, but it may take
months or years for this damage to become clinically apparent [4]. It has been proposed that anthracycline-related cardiac toxicity is characterized by a greater tendency to be irreversible secondary to cardiac cell death, which is referred to as type I cardiotoxicity [8].

In the adjuvant setting, three main studies have tried specifically to investigate the long-term (>8 years) cardiac outcomes of women treated with anthracycline-based regimens (Table 1) [9–11]. The first was reported by an Italian group in Milan, which analyzed 1000 patients enrolled in three prospective trials comparing different doxorubicin-based regimens with CMF [9]. The median cumulative dose of doxorubicin in these studies was 294 mg/m². At a median follow-up of 11 years after chemotherapy completion, the cumulative cardiac mortality for the whole population was 0.6% for doxorubicin-treated patients and 0% for CMF-treated patients. Of 1000 patients, ~50% were known to be alive and free of disease, of which 75% consented to undergo cardiological evaluation using 12-lead electrocardiogram (ECG) and echocardiogram. In this subgroup (n = 355), systolic dysfunction was higher in those previously treated with doxorubicin compared with those who received CMF (8% versus 2%).

A French group later investigated the long-term cardiac safety of six cycles of FEC100 (5-fluorouracil, epirubicin 100 mg/m², and cyclophosphamide), which is widely used in Europe nowadays [10]. After a median follow-up of 8 years, 278 disease-free patients of 565 patients with early-stage breast cancer randomly assigned to receive either six cycles of FEC50 (epirubicin 50 mg/m²) or FEC100 in the adjuvant setting were eligible for cardiac function evaluation. Of the 278 eligible patients, 65 patients treated with FEC50 and 85 patients who had received FEC100 were cardiologically assessed by clinical examination, ECG and left ventricular ejection fraction (LVEF) measurement by radioisotopic or ultrasonographic methods. Two of 85 patients (2.3%) receiving FEC100 had CHF and another 18 patients developed asymptomatic drop in LVEF; in contrast, only 2 patients treated with FEC50 experienced asymptomatic drop in LVEF.

A more recent analysis from a large Southwest Oncology Group (SWOG) study examined a similar question [11]. A total of 180 breast cancer survivors from a potential sample of 1176 patients were analyzed to compare the long-term cardiac safety of an adjuvant CAF (cyclophosphamide, doxorubicin 60 mg/m², and 5-fluorouracil) regimen with CMF for a total of six cycles. At a median follow-up of 5–8 years following therapy, the mean LVEF measured by multigated acquisition (MUGA) scan in the doxorubicin group was significantly lower than that of the CMF-treated patients (61.4% versus 64.8%, respectively; P = 0.01). However, no difference was found at 10–13 years of follow-up in a smaller group of 17 patients (63.4% versus 62.8%, respectively; P = 0.64).

Despite the apparent low incidence of late cardiac events in patients treated with anthracycline-based regimens in the adjuvant setting, these data should be interpreted with caution. These retrospectively designed studies likely underestimate the true incidence of cardiac events as important data on patients who relapsed and/or died earlier are missing and could consequently affect the results. This is supported by the high incidence observed in the Surveillance, Epidemiology, and End Results (SEER) database in which up to 38% of elderly breast cancer patients (>65 years) at 10 years of follow-up after treatment with an anthracycline-based regimen developed CHF, compared with 32% and 29% for those treated with nonanthracycline-based regimens and no chemotherapy, respectively [12].

Every effort should be made to restrict the cumulative dose of anthracyclines to no greater than 360 mg/m² for doxorubicin and 720 mg/m² for epirubicin. Special attention should be given to elderly patients (>65 years) and those with relatively low LVEF at baseline (50%–55%). In a prospective, blinded, observational Danish study, 70 of 120 patients (58%) experienced a 25% relative reduction in LVEF 3 years after treatment with an adjuvant epirubicin-based regimen.

### Table 1. Summary of three large studies that address the long-term cardiac toxicity of different anthracycline-based regimens in adjuvant breast cancer

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<tbody>
<tr>
<td>No. of patients</td>
<td>355</td>
<td>150</td>
<td>180</td>
</tr>
<tr>
<td>Anthracycline used</td>
<td>Doxorubicin</td>
<td>Epirubicin</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Cumulative dose of</td>
<td>294</td>
<td>600 (n = 85); 300 (n = 65)</td>
<td>360</td>
</tr>
<tr>
<td>anthracycline (mg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of cardiac evaluation (years)</td>
<td>11</td>
<td>8</td>
<td>5–8; 10–13</td>
</tr>
<tr>
<td>Method of evaluation</td>
<td>ECG, echocardiogram</td>
<td>ECG, echocardiogram</td>
<td>MUGA scan</td>
</tr>
<tr>
<td>Results</td>
<td>8% systolic dysfunction with A (versus 2% for CMF)</td>
<td>2/85 (2.3%); CHF in high-dose epirubicin</td>
<td>5–8 years: LVEF (61.4% versus 64.8% for A and CMF, respectively; P = 0.01)</td>
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<td></td>
<td>18 versus 2 patients with asymptomatic LVEF drop</td>
<td>10–13 years: LVEF (62.8% versus 63.4% for A and CMF, respectively; P = 0.64)</td>
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</table>

*Clinical cardiac evaluation was carried out in all three studies.

ECG, electrocardiogram; MUGA, multigated acquisition; A, anthracycline; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; CHF, congestive heart failure; LVEF, left ventricular ejection fraction.
(cumulative dose 850–1000 mg/m²). More importantly, 20% of them progressed to develop CHF [13]. This emphasizes that patients treated with adjuvant anthracycline-based regimen remain at high risk on the long term and thus continuing cardiac monitoring beyond the chemotherapy treatment period appears rational.

There are no clear guidelines on the optimal intervals and total duration of cardiac monitoring. A recent analysis of the SEER database has shown that CHF rates continue to increase up to 10 years after treatment for women >65 years who received anthracycline-based regimens [12]. Hence, in the absence of progressive LVEF decline, it is reasonable to consider annual cardiac monitoring for a minimum of 5 years for young women who were treated with an anthracycline-based regimen. In elderly women and/or those with progressive LVEF decline over time, cardiac monitoring may even continue for 10 years or more, as clinically indicated. Nevertheless, investigating the robustness and usefulness of prolonged cardiac monitoring in the context of a randomized clinical trial would further clarify the validity of this approach and its impact on patients’ morbidity and mortality.

Several methods have been described to reduce the risk of anthracycline-related cardiac toxicity. Weekly dosing and prolonged infusion have been shown to be associated with reduced risk for LVEF drop and CHF [4]. Thus, these strategies remain an option in patients more vulnerable to cardiac toxicity from anthracyclines (e.g. old age, comorbidities). In contrast, pegylated liposomal doxorubicin has emerged as a more refined preparation with significantly lower risk for cardiac events [14]. In the metastatic setting, several phase III randomized trials with this agent have shown at least equivalent efficacy with lower cardiotoxicity compared with conventional doxorubicin [15–17]. Currently, a large phase III trial coordinated by the International Breast Cancer Study Group (IBCSG 32-05/BIG 1-05) is evaluating the role of liposomal doxorubicin in elderly women with endocrine-nonresponsive adjuvant breast cancer who are not fit for standard therapy. Although the study was prematurely stopped due to slow accrual, however, the results could provide us with some insights regarding a potential role for liposomal doxorubicin in the elderly population.

Dexrazoxane remains the sole cardioprotective agent proved to decrease anthracycline-induced cardiomyopathy for both doxorubicin and epirubicin [18, 19]. It seems equally cardioprotective when given to patients before the first dose or even after they have reached the cumulative toxicity dose [20]. Marty et al. [21] conducted a randomized phase III clinical trial addressing the effect of adding dexrazoxane to an anthracycline-based regimen in patients previously exposed to anthracyclines. Those who received dexrazoxane experienced significantly fewer cardiac events (13% versus 39%; \( P < 0.001 \)) and a lower and less severe incidence of CHF (1% versus 11%; \( P < 0.05 \)). Furthermore, the addition of dexrazoxane did not seem to affect the response rate to anthracyclines. Although the latter point had been challenged in an earlier study that showed reduced response rate in the dexrazoxane-treated patients [18], subsequent randomized trials failed to show this observation [21, 22].

As far as treatment is concerned, angiotensin-converting enzyme (ACE) inhibitors are the most investigated, although evidence for their efficacy remains weak [23]. In the prospective observational study by the Danish group described previously, patients who developed significant LVEF decline during epirubicin-based therapy and were treated with ACE inhibitors had remarkably potent and long-lasting recovery when compared with the untreated group (\( P < 0.001 \)) [13]. Later studies have suggested that the addition of beta-blockers to ACE inhibitors could further improve clinical outcomes [24, 25]; however, further validation is required.

Taxanes have been incorporated in adjuvant treatments for breast cancer patients in the 1990s. Hence, there is lack of sufficiently long-term cardiac safety data. However, in the short term, it does not appear to increase anthracycline cardiotoxicity. A trial comparing doxorubicin (75 mg/m²) followed by CMF with the combination of paclitaxel and doxorubicin (60 mg/m²) followed by CMF found a similar incidence of symptomatic cardiac events at 31 months (0.5% versus 0.3%, respectively) [26]. Similar results were obtained in the Breast Cancer International Research Group (BCIRG 001) study, which compared FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) with TAC (docetaxel, doxorubicin, and cyclophosphamide), both given for six cycles [27]. At a median follow-up of 5 years, the incidence of mild to severe CHF was 0.1% in both arms. Furthermore, a nonanthracycline-containing regimen, TC (docetaxel 75 mg/m² and cyclophosphamide 600 mg/m²), did not show an increased risk for cardiac events when compared with AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²) at 7 years of median follow-up [28]. In contrast, comparing six cycles of FEC100 with three cycles of FEC100 followed by three cycles of docetaxel showed a significantly higher incidence of cardiac events at a median follow-up of 5 years (1.3% versus 0.4%; \( P = 0.03 \)) [29].

### Secondary Cancers

The increased use of cytotoxic agents to treat breast cancer has raised awareness within the medical community of secondary cancers as possible long-term sequelae. Besides the risk of developing new contralateral disease, population-based studies have clearly shown that breast cancer survivors remain at an increased risk of developing a secondary non-breast cancer (SNBC) [30, 31]. It is estimated that 1 in every 20 patients will develop an SNBC in 10 years, which corresponds to a 22% increase in the relative risk [30]. Some of this risk is related to genetic predisposition (BRCA2 and p53 carriers), radiotherapy (e.g. risk for secondary lung and esophageal cancer), and hormonal therapy (e.g. risk for uterine cancer secondary to tamoxifen); nevertheless, chemotherapy has been linked particularly to the development of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [30–33].

Several studies have reported an increased risk for AML and MDS in breast cancer patients treated with adjuvant chemotherapy (Table 2) [32, 34, 35]. Arguments supporting this association have been strengthened by signature chromosomal aberrations and evidence of dose–response...
relationships after exposure to alkylating agents and topoisomerase II (topo II) inhibitors [36]. It remains unclear, however, whether therapy-related AML represents a truly stochastic event, or if individuals have different degrees of susceptibility [37]. AML related to alkylating agents typically develops after 5 years of initial treatment, is often classified as M1 or M2 with abnormalities in chromosomes 5 and 7, and has a poor prognosis. In contrast, AML related to topo II inhibitors typically develops within 5 years of therapy and is frequently associated with 11q23 cytogenetic abnormality [38].

In an attempt to assess the risk of developing AML and MDS following exposure to epirubicin-based regimens, Praga et al. [32] reviewed 7110 patients treated with epirubicin and cyclophosphamide in 19 randomized clinical trials. At a median follow-up of 8 years, the cumulative probability of AML or MDS was 0.55%. However, the risk increased in relation to the cumulative doses of both agents. Patients who received cumulative doses not exceeding those used in standard regimens (720 and 6300 mg/m², for epirubicin and cyclophosphamide, respectively) had an 8-year probability of 0.37% [95% confidence interval (CI) 0.13% to 0.61%] compared with 4.97% (95% CI 2.06% to 7.87%) for those who received higher doses. Similar results were obtained with doxorubicin-based regimens [34, 39]. A combined analysis of six adjuvant studies conducted by the National Surgical Adjuvant Breast and Bowel Project group using AC reported a 5-year incidence of AML ranging from 0.3% to 1.2% [34]. Higher risk was associated with greater dose intensity. A possible explanation, apart from the higher cumulative doses of the drugs, is the use of granulocyte colony-stimulating factors (G-CSFs) with the dose-intense regimens. An analysis based on the SEER database showed that the addition of G-CSF to adjuvant chemotherapy doubles the risk of developing subsequent AML or MDS when compared with chemotherapy alone [40]. However, the absolute risk remains low.

The leukemogenic effect of G-CSF is a subject of considerable controversy, which remains unresolved. Patt et al. [41] failed to find an increased risk for AML in elderly breast cancer patients (>65 years), in whom G-CSF was administered during the first year after breast cancer diagnosis. The same was observed in the Cancer and Leukemia Group B 9741 phase III trial in which patients randomly assigned to receive dose-dense regimens with filgrastim support had no increased risk of developing AML or MDS compared with those receiving the same regimen at conventional periods with no G-CSF [42]. Furthermore, data from the National Marrow Donor Program® showed that only 20 of 4015 healthy donors who were exposed to G-CSF for the purpose of peripheral blood stem cell collection developed cancers, which is comparable with the population-based incidence of leukemia [43].

The risk for AML appears negligible in patients treated with CMF, provided that cyclophosphamide is given at standard doses [33]. As for taxanes, a SEER database analysis [41] and data from large adjuvant trials have not shown an increased risk with paclitaxel or docetaxel [28, 29, 35]. A 7-year update of a study comparing AC with TC showed no secondary leukemia in the TC arm, when compared with 2 of 510 cases (0.4%) in the AC arm [28]. A three-arm study comparing the Canadian CEF (cyclophosphamide 75 mg/m² days 1–14, epirubicin 60 mg/m² days 1 and 8, and 5-fluorouracil 500 mg/m² days 1 and 8) with 2-weekly dose-dense EC (epirubicin 120 mg/m² day 1 and cyclophosphamide 830 mg/m² day 1) followed by paclitaxel (175 mg/m² day 1) and with 3-weekly AC followed by paclitaxel showed that ∼0.5% of patients developed AML in the first two arms [35]. This is mainly attributed to the high cumulative dose of epirubicin and perhaps the use of G-CSF. However, no secondary leukemia was diagnosed in patients randomly assigned to the AC paclitaxel arm.

Hence, in clinical practice, the risk of leukemia is likely to be very low if the cumulative doses of anthracyclines and cyclophosphamide are not exceeded. Clinical trials attempting to improve therapeutic benefit by dose escalation need to take the resulting increased risk for leukemia into account when assessing potential benefit and risk. The use of G-CSF could possibly add to this risk and its use should therefore be limited to the settings in which strong evidence is available.

cognitive function and neurotoxicity

During the past two decades, there has been increased interest in the cognitive effects of chemotherapy, particularly in breast cancer patients treated in the adjuvant setting. The incidence of cognitive impairment secondary to chemotherapy remains unclear, but it is estimated to be in the range of 20%–30% of all treated patients [44]. An early study by Ahles et al. [45] showed that breast cancer survivors who were treated with systemic chemotherapy (>5 years earlier) have significantly lower scores of psychomotor functioning, and verbal and working memory. Other studies showed similar observations after shorter follow-up [46, 47]. A meta-analysis involving around 450 women treated with adjuvant chemotherapy further confirmed this association [48]. However, these studies have been criticized about different aspects of their methodologies, including heterogeneity in the types of chemotherapy given and methods.

### Table 2. Incidence of AML/MDS in breast cancer patients following adjuvant chemotherapy

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<tr>
<th></th>
<th>Praga et al. [32]</th>
<th>Smith et al. [34]</th>
<th>Burnell et al. [35]</th>
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<tbody>
<tr>
<td>Year of publication</td>
<td>2005</td>
<td>2003</td>
<td>2010</td>
</tr>
<tr>
<td>Cumulative dose (mg/m²)</td>
<td>Group A: E ≤720; C ≤6300</td>
<td>AC: 240/2400</td>
<td>CEF: 6300/720/300</td>
</tr>
<tr>
<td></td>
<td>Group B: E &gt;720; C &gt;6300</td>
<td>High dose</td>
<td>EC-P Q2W: 480/3320/700</td>
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<tr>
<td></td>
<td></td>
<td>C: 24800</td>
<td>AC-P: 240/2400/700</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>Incidence (%)</td>
<td>8 years</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>Group A: 0.37</td>
<td>Group B: 4.97</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>30.4 months</td>
<td>High dose</td>
<td>C: 1.01</td>
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E, epirubicin; C, cyclophosphamide; AC, doxorubicin and cyclophosphamide; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; EC, epirubicin, cyclophosphamide, and paclitaxel; Q2W, once every 2 weeks.
of assessing cognitive function, and in the length of time since chemotherapy completion [49]. Moreover, the majority of these studies failed to control for the potential effects of mood, menopausal changes, and adjuvant hormonal therapy on cognitive function. Thus, a second generation of prospective longitudinal studies has been conducted in the past five years in an attempt to address the same questions in a more robust manner.

Following surgery, it has been found that breast cancer patients experience a significant deterioration of their subjectively rated cognitive function, QoL, and psychological well-being yet with no impairment observed on carrying out neurophysiological tests [50]. Thus, breast cancer diagnosis per se appears to exert a subjective rather than an objective effect on cognitive function. In this context, Debess et al. [51] recently reported the results of a prospective longitudinal study in which cognitive function was examined following surgery and 6 months thereafter in 120 breast cancer patients. Seventy-five patients received adjuvant chemotherapy (FEC), 26 received tamoxifen, and the remaining 19 patients were not treated with adjuvant systemic therapy. These patients were then compared with 208 healthy age-matched controls. The results showed no major changes over time, nor did they identify a difference with respect to using objective tools (i.e. neurophysiological test battery) between patients who underwent chemotherapy and those who received no medical treatment. However, all patients improved on most measures of cognitive function that evaluated their subjectively rated level of cognitive and psychological distress. Of note, while breast cancer patients who did not receive adjuvant therapy reached a level similar to that of the controls 6 months after surgery, those treated with tamoxifen or chemotherapy showed some improvement, although their cognitive functions remained impaired when compared with controls. Other studies, however, confirmed the lack of detrimental effect of chemotherapy (particularly epirubicin-based regimens) on cognitive function measured up to 18 months following breast cancer diagnosis [52–54].

It is difficult to draw solid conclusions from the available literature in this field. It appears that earlier studies suffered some limitations in their design, which resulted in overestimating the effects of chemotherapy on cognitive function. Later studies have shown that patient reports of cognitive symptoms after chemotherapy are strongly associated with fatigue, anxiety, depression, and impaired QoL [44]. But these variables are not associated with neuropsychological performance on formal tests.

Another prospective longitudinal study failed to show any detrimental effect of chemotherapy on neurophysiological tests apart from poor motor function, which was suggested to be related to motor neuropathy secondary to chemotherapy [55]. This is of interest, given the increasing use of taxanes in the adjuvant setting. Taxanes produce symmetrical, axonal mixed, distal neuropathy, while central toxicity remains extremely rare for these agents [56]. Detailed discussion on neurotoxicity is available online only (supplementary data, available at *Annals of Oncology* online).

There are no proven interventions for preventing or treating chemotherapy-related cognitive impairment. Small randomized studies of erythropoietin, modafinil, and other agents have failed to show convincing improvement in cognitive function [57–59]. Currently, a number of cognitive rehabilitation studies are under way in addition to studies using magnetic resonance imaging to evaluate changes in cognitive performance before and after adjuvant chemotherapy. To obtain robust recommendations, future studies should be prospective and longitudinal in design, with appropriate control groups assessed in the same way to draw solid conclusions [60].

### premature menopause, pregnancy, and breast-feeding

Around 6% of patients in the developed world and 25% of patients in the developing world are diagnosed with breast cancer below the age of 40 years [61, 62]. These young women have poorer survival and a higher risk for recurrence compared with their older counterparts [63]. However, advances in the field of adjuvant therapy have improved breast cancer survival and significantly reduced the risk for recurrence, with 400 000 breast cancer survivors <40 years estimated in the United States in 2010 [64]. Given the rising trend of delaying pregnancy to later in life [65], more women are diagnosed with breast cancer before completing their families. Therefore, patient enquiry into the possibility of subsequent pregnancy is commonly encountered nowadays in breast cancer clinics.

Chemotherapy has been shown to induce menopause, which can be either temporary or permanent [66]. The risk for chemotherapy-related amenorrhea (CRA) depends mainly on the patient age, type of chemotherapy, and the total number of cycles administered [67]. An earlier analysis of two IBCSG studies has demonstrated that the higher the age at diagnosis and the higher the number of chemotherapy cycles, the lower the age of developing menopause [68]. Table 3 summarizes the incidence of CRA according to patient age and the type of chemotherapy regimen [66, 68–72] and further information on CRA is available online only (supplementary data, available at *Annals of Oncology* online).

While we are still lacking a standardized procedure for fertility preservation, a considerable number of women who were previously treated with adjuvant chemotherapy manage to get pregnant afterward. Available evidence clearly suggests that

<table>
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<tr>
<th>Table 3. Risk of chemotherapy-related amenorrhea according to age</th>
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<tr>
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<tr>
<td>None [66]</td>
</tr>
<tr>
<td>AC × 4 [66, 67, 70]</td>
</tr>
<tr>
<td>CMF × 6 [68, 69, 71]</td>
</tr>
<tr>
<td>CAF/CEF × 6 [69, 71]</td>
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<tr>
<td>AC × 4, P × 4 dose dense; AC × 4, PT × 4 (then T × 1 year) [72]</td>
</tr>
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AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; P, paclitaxel; T, trastuzumab.
pregnancy is safe and does not seem to adversely affect breast cancer outcome [73–76]. However, the concern remains whether the previously received chemotherapy could have a detrimental effect on the course of pregnancy, fetal outcome, or subsequent breast-feeding. Two large studies have assessed the fetal outcome in women with history of breast cancer [77, 78]. In a large Danish study, 216 women who became pregnant following breast cancer diagnosis were compared with a large cohort of 21 195 women without breast cancer [77]. The mean gestational age at delivery was 39 weeks in both groups, with similar risks for preterm delivery, low birth weight, and congenital anomalies (6%, 1.5%, and 3.4%, respectively). By contrast, a larger Swedish population-based study has suggested that pregnancy in women with a history of breast cancer should be regarded as ‘high risk’ [78]. In this study, 331 women who first gave birth at a mean time of 3 years following breast cancer diagnosis were identified out of a total number of 2 870 932 births registered in the Swedish database between 1973 and 2002. The large majority of births from women previously treated for breast cancer had no adverse events. However, this group was associated with an increased risk for delivery complications [odds ratio (OR) 1.5, 95% CI 1.2–1.9], cesarean section (OR 1.3, 95% CI 1.0–1.7), very preterm birth (<32 weeks) (OR 3.2, 95% CI 1.7–6.0), and low birth weight (<1500 g) (OR 2.9, 95% CI 1.4–5.8).

There is no evidence that chemotherapy affects the quality of breast milk in women with a history of successfully treated breast cancer. Limited available evidence suggests that breast-feeding is safe and feasible; however, it is associated with significant challenges [79, 80]. Several small studies have shown that ~50% of patients treated with breast-conserving surgery and radiotherapy experience limited postnatal milk production from the ipsilateral breast [81, 82]. However, this is mainly related to radiotherapy-induced fibrosis rather than chemotherapy. The fact that women can successfully breast-feed from the contralateral breast argues against the persistence of systematic adverse effects of the previously received chemotherapy. This has been confirmed by a recent, small retrospective series of 20 patients with successful long-term breast-feeding, despite having been previously treated with novel anthracycline-based regimens [83].

sexuality

Sexuality is a biophysical experience and remains vital to the psychological well-being and QoL of breast cancer survivors. Sexual intimacy has been found to make the experience of cancer more manageable and assist in the recovery process [84]. While cancer can have an impact on sexuality across the whole range of cancer types [85], breast cancer has a number of unique consequences because of the breast being a signifier of feminine sexuality and its role as a source of erotic pleasure and stimulation.

In fact, there is compelling evidence that breast cancer has a significant impact on a women’s sexuality, both physically and psychologically. Ganz et al. [86] conducted a large longitudinal study in the late 1990s addressing the sexual health of women after the diagnosis of breast cancer. They found that problems with body image and sexuality occurred during or after treatment, and although problems with body image improved with time, sexual problems continued up to 5 years. Later studies made similar observations but with shorter follow-up [54, 87]. Sexual dysfunction appears to be much more prevalent in women who receive chemotherapy and among younger women who are more vulnerable to changes in ovarian function and to body image concerns [86, 88].

Recently, an Australian group conducted a systemic review of literature addressing the changes in sexuality following breast cancer from different perspectives, including sexual function, impact of physical changes, and sociocultural issues [89]. The results clearly showed that women who undergo adjuvant chemotherapy are at higher risk for sexual dysfunction than those who have not received such treatment. It was most significantly associated with problems of arousal, lubrication, orgasm, and sexual pain. The problem tends to be more severe in young women if chemotherapy has resulted in premature menopause. Not surprisingly, several factors related to physical and emotional status have been shown to affect sexuality, including negative body image, feelings of sexual unattractiveness, loss of femininity, depression, and anxiety. No considerable differences were witnessed between women in Western nations and those in the Middle East and Asia regarding sexuality following breast cancer diagnosis [89].

Current evidence suggests that sexuality is often not addressed with breast cancer patients and, even when discussed, it is done at an unsatisfactory level [90, 91]. Ganz et al. [92] noted that interest in sexual activity is one of the most relevant problems regarding QoL issues that remains altered over time. Acknowledging this fact, health professionals should properly counsel their patients on issues related to sexuality and intimacy, and address their unmet needs in this arena.

conclusions

As cancer treatment goals shift from mere improvement in overall survival to maintaining better QoL, more attention should be paid to long-term chemotherapy-related toxic effects. Elderly breast cancer survivors remain more prone to long-term cardiac toxicity and secondary leukemia. However, the absolute risk is low and is closely linked to the cumulative dose of anthracyclines and alkylating agents; the latter being related to the risk for secondary leukemia. Concerns related to fertility and sexuality remain paramount to young breast cancer survivors, and proper and early counseling is needed to address these issues adequately [93].

It is important to realize that our role as oncologists is not only to treat the tumor but also to improve the QoL of our patients. Considering that the absolute benefit of adjuvant chemotherapy on overall survival is not uniform across different breast cancer molecular subtypes, more effort should be invested in delivering these agents to the right patient populations. This would benefit those who really need chemotherapy, while sparing others from potentially devastating long-term adverse events and associated reduction in QoL. Currently, there is a paradigm shift in the way adjuvant chemotherapy is prescribed considering the biology of the tumor and not only the staging parameters (e.g. tumor size, nodal status) [94]. Recently, the Breast International Group
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and the North American Breast Cancer Group launched a task force to prospectively collect information addressing the long-term toxic effects (5–10 years) of different chemotherapy regimens administered in the adjuvant setting. The outcome of these efforts will enable us to refine our understanding and help us in implementing preventive and management strategies in this field.

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disclosure

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