Adjuvant Chemotherapy in Breast Cancer

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Introduction

The biological rationale for adjuvant systemic therapy is to eradicate micrometastases and therefore improve patient outcomes. Adjuvant combination chemotherapy regimens result in a significant reduction in risk of 5-year recurrence and 15-year mortality rates, with a greater benefit in women <50 years of age [1]. In the clinical setting, the decision to use adjuvant chemotherapy is guided by the clinician's estimation of the patient's prognosis (both her risk of cancer recurrence and overall life expectancy) and assessment of the chemosensitivity of the tumor. Not surprisingly, the use and choice of adjuvant chemotherapy regimen in clinical practice are highly variable. Prognostic determinants of breast cancer recurrence may be broadly divided into the categories of tumor stage (including both tumor size and nodal status) and tumor biology (such as tumor grade, estrogen receptor (ER), progesterone receptor (PR) status, and HER2/neu expression).

It is important to note that the relapse risk for small tumors is relatively small, and it is important to consider the limited benefits in this patient subgroup in the context of the potential risks of toxicities with systemic chemotherapy. Substantial progress has been made in our current understanding of the genes involved in breast cancer, with gene profiling techniques confirming the biological heterogeneity of breast cancer at a molecular level. Researchers have identified at least two intrinsic luminal subtypes (luminal A and luminal B) with distinct gene expression, a basal-like subtype, comprised of primarily triple-negative breast cancer (TNBC, defined as ER negative, PR negative, and HER2/neu negative), and a HER2/neu-positive subtype [2, 3]. Broadly speaking, strongly hormone receptor (HR)-positive tumors are considered less chemosensitive than HR-negative breast cancers [4], with the degree of HR positivity thought to correlate with endocrine therapy responsiveness. As such, the optimal use of adjuvant chemotherapy in HR-positive breast cancer has become quite complex [5]. The identification of the specific subgroup of patients with HR-positive tumors that will benefit the most from adjuvant chemotherapy remains a major challenge to clinicians at present.

Prospective data on the utility on biomarkers to predict chemosensitivity are limited, with the most promising biomarkers likely to be multigene prognostic signatures that are able to capture the multiple biological pathways that determine chemotherapy response. The earlier National Institute of Health (NIH) clinical guidelines on adjuvant therapy have recommended chemotherapy for those patients with tumors >1 cm and in the presence of involved nodes [6].

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However, recent advances in our understanding of breast cancer have resulted in several revisions to these guidelines, taking into account the tumor biology of breast cancer.

This chapter will focus on the use of adjuvant chemotherapy primarily in the HER2/neu-negative subtype of breast cancer. HER2-directed therapy will be covered in detail in a separate chapter. The regimens that will be discussed are used in both the ER-positive and triple-negative breast cancer (TNBC, defined as ER-negative, PR-negative, and HER2/neu-negative) subtypes and in both preoperative (neoadjuvant) and adjuvant settings. Specifically, the use of biomarkers and multigene tests to identify the subset of patients with HR-positive breast cancer will be discussed in detail. Finally, we will also discuss special considerations for the use of adjuvant chemotherapy in the setting of inflammatory breast cancer, elderly, young, and pregnant patients and will conclude with a discussion on the management of chemotherapy-associated toxicities.

Standard Chemotherapy Regimens

The choice of an adjuvant chemotherapy regimen should take into account the tumor burden and breast cancer subtype, as the absolute reduction in the risk of recurrence and mortality from adjuvant chemotherapy is dependent upon the baseline risk. There are a number of commonly utilized adjuvant chemotherapy regimens in clinical practice today (Table 23.1), with most typically given over 4–8 cycles in total. As many of these regimens have not been compared head to head in clinical trials, there is currently no single uniformly accepted standard adjuvant chemotherapy regimen.

Commonly used regimens for breast cancer are summarized in Table 23.1 *and can broadly be divided into:*

1. Non-anthracycline-containing regimens (i.e., CMF and TC)
2. Anthracycline-containing regimens (i.e., AC, FAC, FEC)
3. Anthracycline- and taxane-containing regimens which incorporate both anthracyclines and taxanes (i.e., AC → T, FEC → taxane and TAC)

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has published a large meta-analysis of different polychemotherapy regimens used in over 100,000 women from 123 randomized trials [1]. The most effective adjuvant chemotherapy regimens included both anthracycline and taxanes, but these were also associated with the highest frequency of toxicity. Overall, the addition of adjuvant chemotherapy reduced breast cancer mortality by about one third, and the proportional risk reductions in the trials analyzed were only minimally affected by age, tumor burden (tumor size and nodal status), tumor grade, ER status, or tamoxifen use.

A summary of the key findings are as follows [1]**:**

- *Standard AC* (*4 cycles*) *and standard CMF* (*6 cycles*) *are equivalent.*
- *Anthracycline-based regimens such as FAC or FEC, which have a higher cumulative anthracycline dosage than standard AC* (*4 cycles*), *are superior to standard oral CMF* (*6 cycles*).
- *The addition of 4 cycles of a taxane to a fixed anthracycline-based control regimen reduced breast cancer mortality. However, there was no significant difference in outcomes when the extra 4 taxane cycles were counterbalanced with extra cycles of a non-taxane chemotherapy.*

More recently, results from the large phase III randomized National Surgical Adjuvant Breast and Bowel (NSABP) B-38 trial were reported, comparing the three adjuvant chemotherapy regimens, dose-dense AC → T, dose-dense AC → T plus gemcitabine, and TAC, in a large cohort of approximately 5,000 patients (65 % with nodal involvement and 80 % with ER-positive disease) [20]. The 5-year DFS and overall survival (OS) rates were similar in all three groups; however, the incidence of grade 3 or 4 toxicity was the lowest with the AC → T regimen.

Another area of variability is the frequency of administering chemotherapy. Dose-dense chemotherapy typically refers to the administration of chemotherapy over a shorter interval. The best example of this is with AC, which can

[AU1] **Table 23.1**

Regimen	Dose	Cycle duration	No cycles	Notes	Reference
Non-anthracycline containing					
Oral CMF	**C**yclophosphamide (100 mg/m^2, PO) d1 to 14 **M**ethotrexate (40 mg/m^2) d1, 8 5-**F**luorouracil (500 mg/m^2) d1, 8	q4 weeks	6	*Nonstandard IV* **CMF** (600/60/600 mg/m^2), d1, 8, q4 weeks is occasionally given	[7–9]
TC	Docetaxel (**T**; 75 mg/m^2) **C**yclophosphamide (600 mg/m^2)	q3 weeks	4		[10]
Anthracycline containing					
AC	Doxorubicin (**A**; 60 mg/m^2)[a] **C**yclophosphamide (600 mg/m^2)	q3 weeks	4	*Dose-dense* **AC** is given q2 weeks with [d]filgrastim support	[9, 11]
FAC	5-**F**luorouracil (500 mg/m^2) **AC** (50/500 mg/m^2)[b]	q3 weeks	6		[12, 13]
CAF	**C**yclophosphamide (600 mg/m^2) Doxorubicin (**A**; 30 mg/m^2)[b] d1, 8 5-**F**luorouracil (500 mg/m^2)	q4 weeks	6	**C** may be given PO at 100 mg/m^2 on d1 to 14 of each cycle	[14]
FEC_{60} (*Canadian*)	5-**F**luorouracil (500 mg/m^2) **E**pirubicin (60 mg/m^2)[c] **C**yclophosphamide (75 mg/m^2, PO) d1 to14	q4 weeks	6		[15]
FEC_{100}	5-Fluorouracil (500 mg/m^2) **E**pirubicin (100 mg/m^2)[c] **C**yclophosphamide (500 mg/m^2)	q3 weeks	6	Filgrastim support should be considered	[16]
Anthracycline and taxane containing					
AC → T	Dose-dense **AC**[a,d] → Paclitaxel (**T**; 175 mg/m^2)	q2 weeks	4 → 4		[17]
	AC → Paclitaxel (**T**; 80 mg/m^2)	q3 weeks → weekly × 12	4 → 12		[18]
FEC_{100} → D	**FEC_{100}** → **D**ocetaxel (**T**; 75 mg/m^2)	q3 weeks	3 → 3		[16]
FEC_{100} → P	**FEC_{100}** → (**T**; 100 mg/m^2)	q3 weeks → weekly × 8	4 → 8		[19]
TAC	Docetaxel (**T**; 75 mg/m^2) **AC** (50/500 mg/m^2)[a, d]	q3 weeks	6		[12]

All chemotherapy is given intravenously unless otherwise stated. Cumulative doses [a]240 mg/m^2, [b]>240 mg/m^2, [c]>300 mg/m^2, [d]Given with filgrastim support

be administered at the same doses in a standard three-weekly interval or a dose-dense fashion every 2 weeks [9, 11]. With treatment administered every 2 weeks, growth factor support with filgrastim is required. With dose-dense AC regimens, paclitaxel may be given following AC either every 2 weeks for 4 cycles or weekly for 12 weeks (at 175 mg/m^2 and 80 mg/m^2, respectively), and it is unclear at this point if either approach is associated with improved outcomes. A recent meta-analysis of dose-dense chemotherapy for early breast cancer, which included 10 randomized trials involving over 10,000 patients, reported a better DFS and OS with dose-dense regimens, particularly in women with HR-negative breast cancer [21].

Chemotherapy in Different Breast Cancer Subtypes

Endocrine therapy forms the basis of adjuvant therapy in patients with HR-positive breast cancer, and the addition of chemotherapy benefits a subset of these patients. In patients with HER2/neu-positive tumors, HER2-directed therapy alone has not been tested in large adjuvant trials, and the addition of chemotherapy to HER2-directed therapy is considered to be the current standard of care in the United States. Finally, for TNBC, there are no targeted therapies recommended for use outside of a clinical trial in the adjuvant setting, again with combination chemotherapy recognized as the standard of care.

Chemotherapy in Hormone Receptor-Positive Breast Cancer

While adjuvant endocrine therapy is the standard of care in patients with tumors that express HRs, the indication for adjuvant chemotherapy in patients with HR-positive disease is undergoing reevaluation. Adjuvant chemotherapy is typically given in sequence with, and prior to, endocrine therapy, as there have been conflicting outcomes with concurrent therapy [22–24]. On average, patients with HR-positive breast cancers derive less benefit from chemotherapy compared to HR-negative tumors [25]. However, there still appears to be a subset of patients with HR-positive tumors that are chemosensitive. The basis for the addition of chemotherapy to adjuvant endocrine therapy is usually guided by the clinician's estimation of prognosis and assessment of the endocrine- and chemosensitivity of the tumor. Patients for whom systemic chemotherapy should be strongly considered include patients with grade 2 or 3 disease, those with high-risk features based upon the gene signature (such as Oncotype DX and MammaPrint), and patients with a higher disease burden. That said, not every patient with node-positive disease has to be treated with chemotherapy, and multigene signatures are particularly useful in guiding the clinicians in regards to the decision to recommend chemotherapy [26].

The EBCTCG overview reported a benefit in terms of 5-year recurrence-free survival with adjuvant sequential chemoendocrine therapy over endocrine therapy alone with hazard ratios of 0.64 and 0.85 in patients with ER-positive tumors aged <50 and >50 years, respectively [27]. The larger impact of chemotherapy in younger patients may be partially explained by the endocrine effect of chemotherapy on ovarian function [6]. Similar long-term DFS benefits with the addition of chemotherapy to adjuvant endocrine therapy were also noted in the phase III randomized NSABP B-20 and Southwest Oncology Group (SWOG) 8814 trials [26, 28]. The identification of predictors of chemosensitivity in HR-positive tumors has been identified as a key challenge.

There is evidence suggesting an inverse relationship between HR expression and chemotherapy benefit in luminal breast cancers. In a study of postmenopausal women with ER-positive and node-positive cancers from the International Breast Cancer Study Group (IBCSG) Trials VII and 12-93, the addition of adjuvant chemotherapy to endocrine therapy improved the DFS (hazard ratio = 0.81, $p = 0.02$, median follow-up of 13 years) [29]. Nonparametric subpopulation treatment effect pattern plot (STEPP) analyses demonstrated that this benefit was limited to the patients whose tumors had low to intermediate levels of estrogen expression. The level of ER appears to predict the response to both endocrine and chemotherapies in opposite directions, but these factors may not entirely overlap. It is likely that there are other biological factors that interact with the ER-signaling pathway to determine chemosensitivity. The assumption that chemosensitivity is inversely related to endocrine sensitivity in ER-positive breast cancer is therefore not clearly defined. Tumors that are endocrine sensitive may also be chemosensitive; conversely, endocrine resistant tumors with poor prognostic factors may not always be chemosensitive.

One biomarker that has been examined in chemosensitive ER-positive tumors is Ki67, a marker of cellular proliferation. In an analysis of 1,521 premenopausal and postmenopausal patients with ER-positive tumors from the IBCSG VIII

and IX trials, respectively, a high Ki67 index was found to be associated with poorer DFS, but did not predict an OS benefit with the addition of chemotherapy to endocrine therapy [30]. The adjuvant chemotherapy used in these trials was CMF and did not include anthracyclines and taxanes. In contrast, a high Ki67 index was predictive of both outcome and benefit to adjuvant taxane chemotherapy in ER-positive breast cancers in subset analyses of the PACS 01 and Breast Cancer International Research Group (BCIRG) 001 trials [31, 32]. An important caveat of these findings is that these were unplanned subset analyses. At this point, Ki67 should not be used as a basis of recommendation for adjuvant chemotherapy outside of a clinical trial setting, at least in part because the test is not always reliable.

A major advancement in the identification of biomarkers of chemosensitivity in HR-positive breast cancers has been the development of multigene prognostic signatures. These are typically derived from high-throughput analyses of tumor specimens for gene expression patterns and subsequently validated in patient cohorts from clinical trials. These assays have the potential to identify subsets of patients that would benefit from the addition of adjuvant chemotherapy to endocrine therapy. The 21-gene assay, called the Oncotype DX (Genomic Health, Redwood City, CA, USA), provides a recurrence score (RS) that predicts for risk of 10-year distant recurrence. The RS is derived from a complex algorithm calculated on the gene expressions of a preselected list of 16 genes of biological interest, including genes involved in estrogen signaling, cell proliferation, and HER2/neu signaling and 5 reference genes for normalization purposes [28]. The utility of the RS as a predictor of distant recurrence risk at 10 years was initially assessed in the NSABP B-14 trial, in which patients with ER-positive, node-negative breast cancer were randomized to receive either tamoxifen or placebo. The RS was shown to more accurately predict for distant recurrence than conventional clinicopathologic characteristics in the tamoxifen-treated patients [33].

The utility of the RS to accurately predict 10-year distance recurrences was demonstrated in a retrospective analysis of the NSABP B-20 trial, in which patients with ER-positive, node-negative breast cancer were randomized to either tamoxifen or tamoxifen plus chemotherapy. Patients with a low or intermediate RS (defined as <18, and ≥18 and <31, respectively) were found not to benefit from chemotherapy, while those with a high RS (defined as ≥31) derived a significant benefit from chemotherapy [28]. The absolute difference in the 10-year distant recurrence rates with the addition of chemotherapy in these RS groups was an increase of 1.1 % and 1.8 % and a reduction of 28.6 %, respectively. Similar results were obtained in a retrospective analysis of the SWOG 8814 trial, in which postmenopausal patients with ER-positive, node-positive breast cancer were randomized to receive either tamoxifen or tamoxifen plus anthracycline-based chemotherapy [26]. One of the primary strengths of this assay is that RNA may be extracted from archived formalin-fixed, paraffin-embedded tissue, which is the primary mode of preserving tissue in most pathology departments.

Another multigene signature with prognostic utility is the FDA-approved 70-gene MammaPrint signature (Agendia, Amsterdam, Netherlands). Unlike the Oncotype RS assay where genes are preselected, MammaPrint was developed using an unsupervised hierarchical clustering approach whereby the high-risk gene signature predicted a poor clinical outcome in tumors of all subtypes [34]. A retrospective analysis of pooled patient cohorts with ER-positive, node-negative breast cancer demonstrated that the 70-gene score had prognostic value and predicted improved survival outcomes with the addition of chemotherapy to endocrine therapy only in the subgroup of 70-gene high-risk patients [35].

While both the Oncotype and MammaPrint assays were tested retrospectively, the Oncotype RS was evaluated retrospectively in a prospectively assembled clinical trial. For this reason, there is far greater confidence, at this time, that the Oncotype assay can reliably predict which patients will benefit from chemotherapy, and even more importantly, which ones will not. In addition, unlike the Oncotype assay, MammaPrint is performed on fresh-frozen

tissue that may limit its feasibility for routine use. Both of these multigene signatures are currently undergoing prospective validation in large ongoing studies (Oncotype RS, TAILORx and RxPONDER trials; MammaPrint, MINDACT trial), which include over 100,000 patients collectively to definitively address their predictive value for chemosensitivity in ER-positive breast cancer [36, 37].

In considering the benefits of adjuvant chemotherapy in patients with HR-positive tumors, it is important to consider common relapse patterns. Patients with HR-positive tumors are at a continued risk of relapse for many years after initial breast cancer diagnosis [38]. More than half of all recurrences among women treated with adjuvant tamoxifen therapy occur between 6 and 15 years after diagnosis, and the greatest benefit with the addition of chemotherapy in DFS was seen primarily within the first 5 years from diagnosis [27]. The limited benefit from chemotherapy in preventing late relapses is also reflected in the DFS patterns of patients with poor prognosis multigene signatures with both the Oncotype RS and MammaPrint assays [28, 39]. Late recurrences and deaths remain a formidable clinical challenge in HR-positive breast cancer, and chemotherapy is unlikely to be the answer to this problem.

The summary recommendations for adjuvant chemotherapy in hormone receptor-positive breast cancer are as follows:

- *Adjuvant chemotherapy should be strongly considered in the setting of node-positive disease, high-grade tumors, and high-risk gene multigene signatures.*
  - *In regard to the utility of the Oncotype DX Recurrence Score:*
  - *The use of Oncotype for node-positive disease is discouraged in poorer prognosis disease, for example, ≥4 positive nodes, or in the setting of high-grade disease, as chemotherapy should routinely be given in these settings.*
  - *The use of chemotherapy is strongly encouraged in patients with Oncotype RS ≥31.*
  - *In node-positive patients, particularly those with one to three positive nodes, consideration can be given to omitting chemotherapy if the Oncotype RS is low (<18) and there are no other unfavorable features.*
  - *Recommendations for patients with intermediate-risk multigene signatures* (i.e., *Oncotype RS 18-31*) *are an area of controversy and active research, and prospective trials in this population are currently underway* [36, 37].

Chemotherapy in HER2-Positive Breast Cancer

The advent of HER2-directed therapy has revolutionized the management of HER2/neu-positive, early-stage breast cancer. Based on the results of five randomized clinical trials, 12 months of adjuvant trastuzumab is now an integral part of systemic therapy for these patients [40–42]. In all studies, trastuzumab was added to a chemotherapy backbone, and there is currently no data to support the use of adjuvant trastuzumab monotherapy. Evidence-based chemotherapy backbones in this context include AC → T (NSABP B-31, NCCTG N9831), AC → docetaxel (BCIRG 006) and docetaxel + carboplatin (BCIRG 006). Given the increased cardiotoxicity risk upon administering trastuzumab concurrently with an anthracycline in the metastatic setting [43], trastuzumab is omitted during the period of anthracycline chemotherapy.

There remains controversy about the treatment of small HER2/neu-positive cancers. There are limited data on outcomes for patients with small, stage I HER2/neu-positive breast cancers because the seminal adjuvant trastuzumab trials excluded patients with these tumors. Current guidelines from St. Gallen and the European Society for Medical Oncology (ESMO) do not recommend adjuvant trastuzumab and chemotherapy for node-negative HER2/neu-positive tumors that are <1 cm [44]. In contrast, the National Comprehensive Cancer Network (NCCN) treatment guidelines have factored in the indirect evidence obtained from retrospective and subset analyses of trials and recommend consideration

be given to the use of trastuzumab-based therapy in T1bN0 tumors, in particular, in the hormone receptor-negative subset [45].

However, there is a wide variation in clinical practice in this subgroup. Recently, interest has developed in using less intensive, and therefore potentially less toxic, partner chemotherapies with adjuvant trastuzumab for low-risk HER2-positive tumors. In a phase II study in women with HER2/neu-positive metastatic breast cancer, weekly paclitaxel and trastuzumab resulted in a 67–81 % response rate, and a 6 % incidence of grade 3 or 4 neutropenia [46]. The Dana-Farber Cancer Institute led a multicenter, phase II, non-randomized study of weekly paclitaxel plus trastuzumab for 12 weeks, followed by maintenance trastuzumab for a further 9 months in patients with node-negative, HER2/neu-positive tumors that are <3 cm (information available at ClinicalTrials.gov; identifier NCT00542451). This trial has completed accrual of 410 patients, of whom approximately 50 % had tumors <1 cm. If the 3-year DFS is >95 %, the regimen will be deemed worthy of further investigation. It is expected that the preliminary results will be available in late 2013.

The adjuvant therapy of HER2/neu-positive breast cancer will be discussed in detail in a separate chapter. The summary recommendations for systemic adjuvant chemotherapy in HER2/neu-positive breast cancer are as follows:

- *Systemic adjuvant chemotherapy should be given in combination with trastuzumab, especially in tumors >0.5 cm.*
- *Trastuzumab is omitted during the period of anthracycline chemotherapy but can be given concurrently with taxanes.*

Preoperative Chemotherapy (Neoadjuvant)

Most early systemic chemotherapy trials for operable breast cancer were conducted in the adjuvant setting, with the use of preoperative (neoadjuvant) chemotherapy limited primarily to inflammatory and locally advanced breast cancer. The original rationale for neoadjuvant chemotherapy (NAC) was to render locally advanced tumors operable by shrinking the diameter of these tumors, thereby reducing the extent of surgery required in operable breast cancer. Studies comparing the adjuvant and NAC approaches have found the survival to be equivalent when using identical systemic agents (Table 23.2). These trials also demonstrated that patients who achieved a pathological complete response (pCR) following NAC had improved clinical outcomes compared to patients who did not.

The NAC and adjuvant chemotherapy regimens used clinically are identical. The NAC approach is now increasingly used in smaller, operable TNBC and HER2/neu-positive tumors, although less commonly with HR-positive tumors as they are inherently less chemosensitive [4, 50]. There has also been a trend by many clinicians to evaluate novel therapies in the preoperative setting. A NAC allows for the study of the biological impact of systemic therapy on pre- and posttreatment tissue and therefore represents a fertile setting for tissue-intensive correlative research. The goal of biomarker discovery in NAC clinical trials is to identify surrogate end points of clinical outcomes, such as predictive biomarkers of therapeutic response or resistance. The US Food and Drug Administration (FDA) is

t2.1 **Table 23.2** Seminal trials comparing neoadjuvant chemotherapy to adjuvant chemotherapy for early-stage breast cancer

t2.2					Neoadjuvant vs. adjuvant therapy			
t2.3	Trial	Chemotherapy	pCR rate (%)	pCR vs. non-pCR hazard ratio	BCS rates	DFS HR	OS HR	Reference
t2.4	NSBAP B-18	AC×4	13	OS: 0.32†	68 % vs. 60 %*	0.93	0.99	[47]
t2.5	EORTC 10902	FEC_{60}×4	3.7	OS: 0.91	35 % vs. 22 %	1.12	1.09	[48]
t2.6	ECTO	AP×4 → CMF×3	20	RFS: 0.43†	65 % vs. 34 %*	1.21	1.10	[49]

t2.7 *BCS* breast cancer survival, *DFS* disease-free survival, *OS* overall survival, *pCR* pathological complete response
t2.8 *$p<0.05$

considering the possibility of using pCR in the NAC setting as a surrogate end point for clinical benefit and as an indication for accelerated drug approval [51].

Practically, NAC should be managed only in a multidisciplinary team setting, with initial assessments made by the breast surgeon and medical and radiation oncologists. Evaluation of treatment response to NAC could potentially allow the treating team to tailor individual treatment based upon tumor response, particularly if there is the suggestion of disease progression. There have been two trials in which patients were randomized mid-treatment to non-cross-resistant chemotherapy regimens according to their mid-treatment response [52, 53]. In both trials, deviating from the initial course of therapy in clinical nonresponders did not increase either the clinical or pathological response rates or improve survival. For operable breast cancer, in the event of disease progression mid-NAC, we would recommend an immediate reevaluation by the breast surgeon in order to assess the feasibility of surgical resection with mastectomy. Decisions about additional chemotherapy can be deferred until the adjuvant setting. For patients with non-resectable disease, radiation or alternative investigational approaches should be considered [54].

Special Clinical Scenarios

Inflammatory and Locally Advanced Breast Cancer

Inflammatory breast cancer (IBC) represents a unique biological entity characterized by distinct clinical and histopathological features, aggressive behavior, and an exceptionally poor prognosis (median survival with current therapy <4 years) [55]. The current standard of care for management of stage 3B IBC is a multimodality approach consisting of NAC followed by surgery and radiotherapy. Achieving a pCR to NAC is the single most important prognostic factor in IBC [56, 57].

Given the relative rarity of IBC, there have been no specific randomized trials examining the optimal NAC regimen, and moreover patients with IBC have historically been excluded from NAC systemic therapy studies due to their poor prognosis. Single-arm studies and retrospective case series show that anthracycline-based regimens are effective (clinical response rates around 70 %) [56] and that their efficacy is enhanced by the subsequent addition of a taxane as evidenced by increased clinical and pCR rates [58, 59]. As such, regimens included in the "Anthracycline and Taxane" section of Table 23.1 are recommended.

Although outside the scope of this chapter, it is noteworthy that approximately 40 % of IBC are HER2/neu positive, and evidence from randomized phase 3 clinical trials strongly supports the routine addition of trastuzumab to NAC in this setting [60].

Elderly Patients

Although the incidence of breast cancer rises sharply with age, there is wealth of quality data discussing the optimal choices regarding adjuvant chemotherapy in the elderly. This is particularly true for patients with advanced comorbidities and frailty, who are generally excluded from phase 3 clinical trials. For this reason, groups such as the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) have developed consensus guidelines specific to the issues facing elderly patients with breast cancer [61]. Compared to their younger counterparts, elderly patients are more likely to present with larger primary tumors and positive lymph nodes [62], at least in part attributable to greater delays in initial diagnosis. Breast cancers in the elderly are also more frequently HR positive [63].

Prescribing adjuvant chemotherapy to elderly patients provokes several unique considerations. First, elderly patients often suffer comorbid illnesses that provide competing mortality risks. As such, determining the potential overall survival gains from adjuvant chemotherapy for an individual patient is more challenging. Groups such as the Cancer and Leukemia Group B (CALGB) have developed tools for pre-chemotherapy geriatric assessment to help address this problem

[64]. It is also important to note that despite competing risks, >40 % of patients diagnosed with breast cancer after the age of 80 will die from breast cancer [65].

Second, elderly patients may be more susceptible to certain chemotherapy toxicities. Although there is no evidence to support modifying chemotherapy doses because of age, strict monitoring of renal and hepatic function during treatment is essential. Furthermore, routine assessment of left ventricular ejection fraction is recommended for patients scheduled to receive anthracyclines. Third, data suggests that elderly patients are more likely to experience difficulties with medication compliance [62], particularly oral medications such as antiemetics. It is thus critical to ensure that patients with any degree of cognitive impairment clearly understand their drug regimens and are adequately educated and supervised if necessary.

There is little prospectively collected, randomized trial data to suggest a particular adjuvant chemotherapy regimen for elderly patients beyond the general standards of care. In general terms, adjuvant chemotherapy is feasible in patients over 65–70 years of age, but increasing age, reduced functional status, and presence of comorbidities are associated with more frequent dose reductions and/or delays [66]. A landmark CALGB study compared standard chemotherapy regimens (either AC or CMF) to oral capecitabine in patients >65 years of age with early-stage breast cancer [67]. The study was stopped early after an interim analysis suggested that the capecitabine regimen was inferior, resulting in an almost doubled risk of recurrence or death. This study reinforces the efficacy of standard chemotherapy in an elderly population. Nonrandomized data also suggest tolerability of the TC regimen patients >65 years [68], although elderly patients do seem more prone to taxane-induced hematological toxicities [69].

Young Patients

Breast cancer in young patients typically demonstrates a worse prognosis and more aggressive phenotype, characterized by higher-grade disease, more advanced stage at initial presentation, and lower rates of HR positivity. While some studies point toward breast cancer in younger patients as having a unique biology [70, 71], others have illustrated that the poor prognosis in younger patients is more a result of higher frequencies of aggressive breast cancer subtypes [72, 73]. The incidence of germline mutations in genes known to predispose to breast cancer is also increased among women <35 years old with breast cancer, with 10–15 % harboring a *BRCA1* and *BRCA2* germline mutation [74]. Diagnosis of a familial breast cancer syndrome has implications for additional treatment decisions including consideration of prophylactic surgeries (i.e., prophylactic mastectomy and/or prophylactic bilateral salpingo-oophorectomy) that have been shown to improve outcomes for this patient population [75, 76].

While general principles for the selection of cytotoxic and targeted agents are quite similar between younger patients and the general population, specific issues that should be considered in prescribing chemotherapy to younger women include the effect of chemotherapy on their future fertility as well as potential long-term toxicities (i.e., cardiac dysfunction and secondary malignancies), which are more relevant in light of their life expectancy. There are a number of options for fertility preservation including oocyte and embryo cryopreservation. Although outside the scope of the current review, all women of childbearing potential facing a diagnosis of BC should be educated on the risk of infertility at the earliest opportunity.

An early referral to a reproductive physician is important, as fertility preservation often involves a delay in the start of adjuvant chemotherapy treatment while the oocytes and/or ovarian tissue are harvested [77]. The return of the ovarian function is dependent on the ovarian reserve and age of the patient, and the relative intensity of the chemotherapy regimen. Testing for ovarian reserve involves the measurement of serum anti-Müllerian hormone and inhibin B levels. The use of gonadotropin-releasing hormone (GnRH) agonists to diminish ovarian function and prevent

damage to ovarian tissue is unproven and is not recommended for this purpose. Finally, it is recommended that sexually active women should be prescribed nonhormonal contraception regardless of menstrual status because they may still ovulate and become pregnant.

Pregnant Patients

Pregnancy and an early-stage breast cancer diagnosis can intersect in one of two ways: Either a patient receiving adjuvant chemotherapy may fall pregnant during treatment or a new diagnosis of breast cancer is made in a pregnant patient. Both require intensive management by a multidisciplinary team including surgeons, oncologists, radiation oncologists, obstetricians, and psychologists. The first of these scenarios is rare, and due to the highly teratogenic effects of systemic cytotoxics during the first trimester, all patients receiving adjuvant chemotherapy should be counseled on appropriate use of contraceptive measures during treatment. In this section, we will discuss the second scenario in more detail.

Like all younger women with breast cancer, patients diagnosed during pregnancy are more likely to have a higher-risk disease [78]. As such, a large proportion of these patients will be candidates for systemic adjuvant chemotherapy. There are no data to suggest that concurrent pregnancy per se is an adverse prognostic factor in early-stage breast cancer [79].

As a general principle, adjuvant chemotherapy regimens should be chosen with the goal of recommending a regimen that is as close to the standard care for nonpregnant patients as possible [79]. The critical issue is the timing of therapy. Systemic chemotherapy should not be prescribed during the first trimester (the period of organogenesis) due to the high risk of fetal malformation. Therefore, in patients diagnosed during this time, options include termination of pregnancy followed by systemic chemotherapy or continuation of pregnancy, delaying the onset of chemotherapy till after 14 weeks of gestation. In patients diagnosed during the second trimester (12–28 weeks), surgery can be followed by adjuvant chemotherapy. In both of these situations, it is prudent to suspend adjuvant chemotherapy at about 35 weeks of gestation, allowing for delivery at about 37 weeks and resumption of any remaining chemotherapy after this. In women diagnosed in the final trimester, it is most sensible to allow for delivery at 35–37 weeks before initiating chemotherapy [79].

The adverse consequences of systemic chemotherapy on fetal health and early child development are reported to be minimal. Deferring treatment till after the first trimester abrogates the risk of fetal malformation. There is a lack of long-term data on the consequences of chemotherapy during pregnancy on subsequent child development, but case series suggest no obvious problems with neurodevelopment or risk of second cancers [79]. Only a small fraction of the total delivered anthracyclines, cyclophosphamide, or taxanes crosses the placenta [80, 81], and together with the altered pharmacokinetics of these drugs in pregnancy [82], exposure of the fetus is thought to be limited. Methotrexate (and hence the CMF regimen) is best avoided to avoid its accumulation in third space fluid compartments. There is limited data on the safety of dose-dense chemotherapy regimens in pregnancy.

Chemotherapy Toxicities

Acute Toxicities

Chemotherapy toxicities are listed in Table 23.3 and can be broadly divided into acute and long-term toxicities. There has been much progress in the management of short-term toxicity, particularly in regard to the prevention and management of nausea and neutropenia. A major development in this area has been the publication of guidelines for the use of effective preventative antiemetic therapies such as dexamethasone, 5-hydroxytryptamine-3 (5-HT3) receptor antagonists (such as ondansetron, granisetron, and palonosetron), and neurokinin 1 (NK1) receptor antagonists (such as aprepitant and fosaprepitant) [83]. Prophylaxis against neutropenia is highly effective. The routine use of prophylactic granulocyte colony-stimulating factors (such as filgrastim and pegfilgrastim) with moderately

t3.1 **Table 23.3** Common chemotherapy-associated toxicities and recommended management

System	Toxicity	Chemotherapy regimens	Management
General	Fatigue	All	
	Weight gain	All	
Ovarian	Vasomotor	All	Gabapentin and SSRIs
	Amenorrhea and infertility	All, especially CMF	Discussion of testing for ovarian reserve, egg, and zygote preservation pre-chemotherapy
Gastrointestinal	Nausea and vomiting	All, especially anthracyclines	Prophylactic antiemetics
	Anorexia	All	
	Mucositis	All	Analgesic mouthwash
	Hepatotoxicity	All	
Skin	Alopecia	All, except CMF	
Hematological	Neutropenia	All, especially dose-dense and docetaxel-containing regimens	Prophylactic filgrastim
	Anemia	All	Replace serum iron, Vitamin B12 and folate if low
		Specific agents	
Cardiac	Congestive cardiac failure	Anthracyclines	Screening of left ventricular ejection fraction in patients >50 years old or with cardiac risk factors
Cancer	Acute myeloid leukemia and myelodysplastic syndrome	Anthracyclines	
Neurological	Peripheral neurotoxicity	Taxanes	
Musculoskeletal	Arthralgia and myalgia	Taxanes	Simple analgesics, NSAIDs

t3.29 Dose reduction and/or delay should be considered standard management for all high-grade toxicities
t3.30 *SSRI* selective serotonin reuptake inhibitor

myelosuppressive chemotherapy regimens, such as dose-dense and docetaxel-containing regimens, markedly reduces the rate of febrile neutropenia, febrile neutropenia-related hospitalizations, and intravenous anti-infective use [84].

Fatigue and weight gain are common general side effects [85] and may be interrelated. Other factors that contribute may include alterations in serum hormonal levels and insulin resistance. Evidence for the health-related benefits of increased physical activity continues to expand [86], and exercise and dietary management is an important aspect of patient care during adjuvant chemotherapy. Another common side effect is decreased ovarian function resulting in menopausal vasomotor symptoms such as hot flashes, mood swings, and decreased ovarian reserve. Selective serotonin reuptake inhibitors (SSRIs) have been used successfully to manage some of the vasomotor symptoms; careful consideration of the use of SSRIs is important in patients on tamoxifen, as some of the SSRIs affect the tamoxifen-metabolizing hepatic enzyme CYP2D6.

Long-Term Toxicities

A comprehensive review of long-term complications of chemotherapy has recently been published by Azim et al. [87]. Cardiac toxicity is especially a concern with anthracycline- and trastuzumab-containing regimens, and the main risk factors are older age, other cardiovascular risk factors, mediastinal radiation, and total dose of anthracyclines received. A number of studies looking at the long-term cardiac toxicity of anthracycline regimens have demonstrated a decrease in cardiac function in up to 11 years of median follow-up, with up to 8 % of anthracycline-treated patients having evidence of systolic dysfunction

compared to 2 % in non-anthracycline-treated patients, although the incidence of symptomatic cardiac failure was only in approximately 10 % of this patient subset [88–90]. In a large population study from the Surveillance, Epidemiology, and End Results (SEER) Medicare database of women >65 years of age with early breast cancer, the adjusted hazard ratio of congestive cardiac failure was 1.26 in women aged 66–70 treated with anthracyclines compared to other chemotherapy regimens, but not in women aged 71–80 [91]. There are potential biases at play in evaluating these administration data sets, and the findings need to be viewed with some caution. It is recommended to restrict the cumulative dose of anthracyclines to no greater than 360 mg/m^2 for doxorubicin and 720 mg/m^2 for epirubicin and to screen patients >50 years of age or with known cardiovascular risk factors with a baseline left ventricular ejection assessment prior to starting anthracycline and trastuzumab therapy.

Acute myeloid leukemia (AML) and myelodysplastic syndrome are uncommon long-term adverse events associated with anthracycline use. A combined analysis of six adjuvant studies with AC conducted by the NSABP reported a 5-year incidence of AML ranging from 0.3 % to 1.2 % [92]. In clinical practice, the risk of leukemia is likely to be very low if the cumulative doses of anthracyclines and cyclophosphamide are not exceeded [93].

Concluding Statements

Although the basic goals of adjuvant chemotherapy for early-stage breast cancer – eradication of disseminated micrometastases to reduce risk of recurrence – remain the same, there have been significant refinements in the way adjuvant therapy is prescribed in the last three decades. Fundamental to these improvements is our ability to estimate (1) the absolute recurrence risk for tumors of varying stages and biological subtypes and (2) the chemosensitivity of individual tumors.

More so now than ever before, it is realized that certain tumors pose a high risk of distant relapse in spite of a relatively smaller tumor burden (i.e., TNBC, HER2-positive tumors). Patients with such tumors may therefore be good candidates for adjuvant chemotherapy in order to reduce this recurrence risk. Conversely, multigene tools with the capacity to predict relative chemosensitivity now allow for the omission adjuvant chemotherapy in a subset of patients with HR-positive breast cancer (regardless of tumor size and possibly nodal status), sparing unnecessary toxicities.

Moving forward, it is unlikely that we will see a large number of phase 3 trials comparing different regimens of conventional cytotoxics in the adjuvant setting. The more pressing questions now are clearly as follows: Which patients derive the greatest relative benefit from adjuvant chemotherapy? Which patients derive little or no benefit from adjuvant chemotherapy and can therefore be spared it? With the advent of newer targeted therapies for certain tumors (e.g., HER2/neu-positive cancers), to what extent can biological therapies replace conventional adjuvant chemotherapy or should the two therapies be given together?

As outcomes for patients with early-stage breast cancer continue to improve incrementally, the conduct of phase 3 clinical trials to evaluate new approaches becomes more challenging. Lower event rates drive the need for higher sample sizes, and it is only through the cooperation of several institutions, often across multiple continents, that we have been able to continue to drive progress. It is difficult to predict the landscape of adjuvant therapy in the next 10–20 years, but research will undoubtedly focus on further tailoring therapy to the individual tumor at hand, taking into account various aspects of histology, biology, and stage.

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Author Queries

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Queries	Details Required	Author's Response
AU1	Please provide caption for Table 23.1.	
AU2	Please check if edit to sentence starting "The absolute difference…" is okay.	