Adjuvant Systemic Therapy

61

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Key Concepts

- Only systemic therapy can eradicate micrometastatic disease and improve long-term disease-free survival
- Evolution of systemic therapy in breast cancer
  - Oophorectomy was the first "systemic" treatment used
  - Thiotepa (single-agent) was shown to increase survival in NSABP protocol #1
  - CMF (Cytoxan, methotrexate, and 5-FU) for 1 year decreased risk of recurrence and became standard in the 1970s
  - Anthracyclines (Adriamycin® and Epirubicin) were demonstrated to be effective
    - Risks include cardiac toxicity and secondary development of leukemia
  - Taxanes (Paclitaxel and Docetaxel) shown effective in combination with anthracycline-containing regimens
    - Dose-dense therapy (every 2 weeks) is more effective than every 3-week therapy
    - Studies continue to determine best regimen, including timing, dose density, duration of therapy, and best drugs
- High-dose chemotherapy with stem cell support may be beneficial, but should only be considered in context of a clinical trial
- Trastuzumab is a targeted therapy, appropriate for women with her-2/neu positive tumors
- For all cytotoxic and targeted therapies, younger women with higher risk node-positive, hormone-negative breast cancer appear to benefit the most
- Triple-negative breast cancers are relatively resistant to chemotherapy

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61

Background

The multidisciplinary treatment of primary breast cancer includes surgery, radiation, and systemic therapy. Approximately two thirds of patients with regional lymph node metastasis recur within 5 years after "curative" resection, presumably due to the presence of undetectable micrometastases that exist at the time of surgery (1). Therefore, only systemic therapy can eradicate micrometastatic disease and improve long-term disease-free survival (2).

Bilateral oopherectomy represented the first systemic "anti-estrogen" therapy for breast cancer. Performed first in a premenopausal patient for recurrent breast cancer in 1895, it resulted in a complete response and survival for 4 years. Overall, oophorectomy results in an approximate 30% response rate (3–5). Ovarian ablation by irradiation and other hormonal treatment options such as adrenalectomy (6), hypophysectomy (7), and high-dose diethylstilbestrol (8) were investigated in the mid-twentieth century. More recently, medical ovarian ablation by LH-RH agonists has become part of adjuvant therapy in premenopausal women (9).

Understanding of the pathophysiology of antiestrogen therapy came later with the discovery of the estrogen receptor (10–12). Tamoxifen was developed in the late 1970s and was studied in clinical trials in the 1980s (13, 14). Over the last decade, the aromatase inhibitors have come into clinical practice in postmenopausal women. Further details of the modern use of hormonal therapy can be found in the chapter on hormonal therapy by Dr. Harold Burstein (Chap. 62).

Cytotoxic Chemotherapy

The evolution of systemic cytotoxic chemotherapy for all cancers started in the 1940s when Louis Goodman and Alfred Gilman observed regression of a non-Hodgkin's lymphoma after injection of nitrogen mustard (15). Folate analogs discovered by Sydney Farber and colleagues became the first chemotherapeutics to induce temporary remissions in ALL and would later be used to treat a variety of cancers including breast cancer (16). In 1955, The Cancer Chemotherapy National Service Center was established at the National Cancer Institute (NCI) in order to screen for potential cancer therapeutic drugs.

The first prospective, randomized trial of adjuvant cytotoxic chemotherapy in breast cancer began in 1958 with the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol no. 1 (17). Eight hundred and twenty six patients underwent modified radical mastectomies and were randomized to placebo vs. adjuvant treatment with thiotepa. In the subset of premenopausal patients with four or more positive nodes involved, 5-year disease-free survival (44 vs. 12 months) and overall survival (57 vs. 24%) were favorably effected by adjuvant therapy.

Combination Chemotherapy

A landmark trial by Bonadonna and colleagues (18) demonstrated that 12 months of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) decreased the risk of recurrence of breast cancer in women with axillary lymph node metastases; at

almost 30 years of follow-up, hazard reductions for relapse and death were 29 and 21%, respectively (19). Henceforth, CMF became the standard adjuvant chemotherapy regimen, with 6 months of "classic" CMF inclusive of oral cyclophosphamide favored over IV CMF (19–22). The benefit of combination chemotherapy has been observed to be greatest in younger women with receptor-negative disease in this and other subsequent trials, and chemotherapy yields additional benefit to antiestrogen therapy in women with receptor-positive disease (9).

Anthracycline-Based Regimens

The anthracycline doxorubicin (Adriamycin®) was approved for the treatment of advanced breast cancer in 1974. Subsequent research then concentrated on defining the optimal CMF regimen (Table 61.1) and deciding whether treatment with doxorubicin improved outcome. The FDA approved Epirubicin, a second anthracycline, only in 1999 for adjuvant treatment of breast cancer. Conclusions from individual randomized trials of anthracycline-containing regimens compared to CMF are mixed with some showing equivalence (23–26), while others suggesting superiority (27–31). The differences in the outcomes may be due to variations in the route of administration, dosing, and duration of CMF, and the specific anthracyclines regimen used.

The EBCTCG overview meta-analysis, which included all relevant randomized trials that began by 1995, revealed a statistically significant benefit of 6 months of polychemotherapy with an anthracycline-based regimen over CMF. Estimates for reduction of annual breast cancer deaths were 38 and 20% in women less than age 50 and 50–69, respectively (32). However, the potential gain with anthracycline-based regimens must also be weighed against the long-term risks of cardiotoxicity and secondary leukemia (33, 34).

Integration of Taxanes

Paclitaxel (Taxol®) trials began in a number of tumors in the 1980s. After demonstrating marked activity in metastatic breast cancer, the FDA approved the use of paclitaxel for recurrent and metastatic breast cancer in 1994.

In the adjuvant setting, the CALGB 9344 trial compared four cycles of paclitaxel 175 mg/m^2 every 3 weeks vs. no further treatment in 3,121 women after four cycles of AC at three different doses of doxorubicin (35). The paclitaxel-treated group experienced significant hazard reductions for recurrence and death at 17 and 18%, respectively. NSABP-B28 compared four cycles of paclitaxel vs. no further treatment after four cycles of AC (36). Patients in the paclitaxel-treated group benefited with a significant 17% hazard reduction in the risk of relapse; however, 5-year overall survival was equivalent at 85%. This study showed no difference in ER-status, as opposed to the CALGB study which demonstrated greater benefit in ER-negative tumors (37). Paclitaxel was approved for the adjuvant treatment of breast cancer in 1999.

Docetaxel (Taxotere®), unlike paclitaxel, does not interfere with the metabolism of anthracyclines. The BCIRG 001/TAX 316 trial compared 6 cycles of FAC vs. TAC every 21 days (fluorouracil vs. docetaxel in combination with doxorubicin and

cyclophosphamide) in 1,491 pre and postmenopausal women with node-positive breast cancer (38). Patients treated with docetaxel experienced significant hazard reductions for recurrence and death at 28 and 30%, respectively, but the incidence of febrile neutropenia was higher in the docetaxel group. Docetaxel was approved in 2004 as adjuvant treatment of operable node-positive breast cancer. Confirming the benefit of docetaxel, the French PACS 01 trial compared 6 cycles of FEC vs. three cycles of FEC followed by three cycles of docetaxel given every 21 days (39). The docetaxel-treated group experienced significant hazard reductions for recurrence and death at 18 and 27%, respectively.

The dosing frequency of combination anthracycline and taxane regimens appears to be important. The National Cancer Institute's Breast Intergroup Trial, INT 9741, showed a benefit of AC to paclitaxel when the drugs were given every 2 weeks (dose dense) vs. every 3 weeks, with significant hazard reductions for recurrence and death at 26 and 31%, respectively (40). The dosing frequency of the taxane irrespective of the anthracycline may also be relevant. ECOG 1199 compared four different taxane regimens after AC × 4 every 3 weeks (paclitaxel or docetaxel weekly for 12 doses or every 3 weeks for 4 cycles) in 4,950 pre- and postmenopausal women with node-positive or node-negative high-risk breast cancer (41). The final prespecified analysis of the taxane or the schedule as an aggregate showed no significant difference. However, secondary comparisons of the standard arm of paclitaxel every 3 weeks vs. the other arms demonstrated hazard ratios favoring paclitaxel given weekly and docetaxel administered every 3 weeks.

The Role of Anthracyclines in the Taxane Era

A US Oncology study compared a nonanthracycline regimen TC (docetaxel, cyclophosphamide) with AC, with each regimen given once every 3 weeks for 4 cycles (42). The TC regimen was associated with a significant 33% hazard reduction for relapse. Overall survival rates were similar for TC and AC at 90 and 87%, respectively ($p = 0.13$). TC is associated with a higher risk of myelosuppression; however, one hopes to avoid the rare but significant long-term complications associated with anthracyclines such as secondary leukemia and cardiotoxicity. Currently, TC is most commonly used in select lower risk node-negative patients and in patients where a nonanthracycline-based regimen is preferred. The US Oncology and BCIRG 006 (43, 44) (see below) studies have led the oncologic community to reconsider the role of anthracyclines. However, further studies are necessary to compare nonanthracycline taxane regimens to other current "third generation" (Table 61.1) regimens such as TAC or dose-dense AC-T. Furthermore, all anthracyclines may not be equal. The 2006 interim analysis of the Canadian NCIC CTG MA.21 study suggested that standard AC-T was less toxic, but significantly inferior to oral cyclophosphamide and IV EF and dose-dense EC-T in terms of 3-year relapse-free survival (85 vs. 90.1 and 89.5%, respectively) (45). However, it is difficult to draw definitive conclusions from this study as similar doxorubicin vs. epirubicin regimens in terms of density were not compared. Clearly, the role of dose density, duration of treatment, and specific role and favored types of anthracycline are still active issues for investigations.

High-Dose Chemotherapy

The majority of early randomized trials of high-dose chemotherapy with stem cell support have failed to demonstrate benefit (46, 47). More recently, two large randomized prospective randomized European studies have shown potential relapse-free and overall survival benefits in patients with high-risk breast cancer (48, 49). High-dose chemotherapy at this time should be considered only in the setting of a clinical trial.

Targeted Therapy-Trastuzumab

Targeted therapy refers to agents that are directed against specific known molecules deemed to be important in the growth or metastatic process of cancer cells. A prime example of this strategy is the development of trastuzumab (Herceptin®), a monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor-2 (HER-2/*neu*, also known as *erb*-B2). HER-2/*neu* overexpression, which occurs in approximately one-quarter of newly diagnosed breast cancers, was first reported as a poor prognosticator by Dr. Slamon and colleagues (50).

Four large phase III trials, the HERA (51), BCIRG 006 (43, 44), NCCTG N9831, and the NSABP B-31 (52) demonstrated marked benefit of trastuzumab when given for at least 1 year in the adjuvant setting for HER-2/*neu* overexpressing disease. All four trials included pre and postmenopausal women primarily with node-positive breast cancer; however, high-risk node-negative patients were also included in all but the NSABP-B31 trial.

The HERA trial randomized 5,090 women receiving adjuvant cytotoxic chemotherapy from a number of acceptable regimens to observation or trastuzumab for 1 or 2 years for every 3 weeks (51). After a median follow-up of 2 years, there was a significant 36 and 34% hazard reduction in the risk of recurrence and death, respectively. Grade 3 or 4 adverse events were more common with trastuzumab (11 vs. 6%), as were fatal grade 5 toxic events, but were still rare (0.5 vs. 0.2%). Severe heart failure only occurred in the trastuzumab group (0.6%).

The two North American Studies, NSABP-B31 and NCCTG N9831, had similar designs (52). NSABP-B31 randomized patients after a standard adjuvant regimen (AC × 4 followed paclitaxel × 4 every 3 weeks (with a subsequent amendment changing the T schedule to 12 weekly doses) to observation or weekly trastuzumab for 1 year. The N9831 trial randomized patients to one of three arms after AC × 4, including weekly paclitaxel for 12 weeks followed by observation or trastuzumab concurrently or sequentially after paclitaxel for 52 weeks. A pooled analysis approved by the NCI was first published in 2005 and updated at ASCO 2007 (52, 53). The most recent update showed that in 3,969 women enrolled in both trials with a median follow-up of 2.9 years, there was a significant 51 and 37% hazard reduction for adjuvant trastuzumab in the risk of recurrence and death, respectively.

The BCIRG 006 was the first phase III study prescribing a regimen without an anthracycline in the modern era of chemotherapy: the study randomized 3,222 women to a control arm of standard AC then docetaxel (AC-T) every 3 weeks for 4 cycles, vs. two trastuzumab-containing regimens, one being the addition of trastuzumab to docetaxel (AC-TH) and the other a nonanthracycline regimen (TCH) (Table 61.2) (43, 44).

Both trastuzumab arms continued treatment for 1 year. The third planned interim analysis in 2009 showed superiority of the both trastuzumab regimens vs. the control arm after 65 months of follow-up. Disease-free survival was 84% for AC-TH and 81% for TCH but was not statistically significant ($p = 0.21$). Overall survival was 92% for AC-TH vs. 91% for TCH and was also not statistically significant ($p = 0.14$). The incidence of cardiac toxicity was significantly higher in patients treated on AC-TH vs. TCH: grade III/IV congestive heart failure was seen in 2 vs. 0.4% of patients ($p < 0.001$) and there was relative decrease in LVEF >10% in 19 vs. 9 % ($p < 0.001$), though the LVEF was still in the normal range for most patients. Acute leukemia developed in 7 patients in the anthracycline arms (0.3%) and in 1 patient in the TCH arm, though the latter was in a patient who received anthracycline treatment for a B-cell lymphoma 20 months prior. The nonanthracycline regimen TCH seems to be comparable to AC-TH and may lead to avoidance of the rare but significant long-term risks of anthracyclines, though data is lacking for comparison to more aggressive regimens such as dose dense therapy.

The optimal length of adjuvant trastuzumab therapy is not yet defined (54). The outcome between patients treated with 1 vs. 2 years of trastuzumab on the HERA study is expected to be available in the near future. Notably, there was a smaller randomized trial conducted in 1,010 women testing docetaxel or navelbine followed by FEC. A subset (232 patients) was treated for HER-2 overexpressing cancers and was randomized to receive or not to receive 9 weekly doses of trastuzumab with either docetaxel or vinorelbine followed by FEC every 3 weeks for 3 cycles (55). Hazard ratio for recurrence or death was 0.58 in the trastuzumab-treated patients, comparable to the larger studies administering at least 1 year of trastuzumab. There is now an ongoing trial evaluating 6 months vs. 1 year of trastuzumab (56).

Overview of Current Standard Treatment Regimens

The decision to use cytotoxic and targeted therapy should be based both on tumor and patient-specific characteristics. Younger women with higher risk node-positive, hormone-negative breast cancer appear to benefit most (32). There are several risk assessment tools currently in use to assist the oncologist and the patient in their decision-making. The web-based risk assessment program Adjuvant! estimates relapse and death risk reduction based on tumor size, lymph node, and hormone status (57). The Oncotype DX™ assay measures the expression of 21 genes-weighed heavily by the expression of ER, PR, and HER2-, by RT-PCR technology, applied to formalin fixed, paraffin-embedded tumors (58). The greatest utility of this assay appears to be helping to identify which women with hormone-positive, node-negative, low-risk tumors might benefit most from chemotherapy in addition to standard hormonal therapy. TAILORx is an ongoing prospective intergroup trial with an accrual goal of more than 10,000 women randomized to adjuvant combination chemotherapy and hormonal therapy vs. hormonal therapy alone based on their Oncotype DX™ recurrence score (59).

Table 61.1 includes select standard adjuvant non-trastuzumab regimens organized by generation (efficacy) similar to that of Adjuvant! It is estimated that second-generation regimens have a relative 15–20% better efficacy than first-generation regimens such as CMF. Third-generation regimens similarly are estimated to have a relative 15–20% better efficacy than second-generation regimens. Table 61.2 includes adjuvant trastuzumab-containing regimens of which direct comparisons are not yet made.

Table 61.1 Select adjuvant nontrastuzumab chemotherapy regimens

Regimen	Number of cycles and duration	Individual drug components, route of admin. and dose in mg/m²				
		Ctx	Mtx	5-FU	Anthracycline	Taxane
First generation						
CMF-oral (23)	6 × 28 days	100 PO d1-14	40 IV d 1,8	600 IV d1,8		
AC × 4 (23)	4 × 21 days	600 IV d1			Doxo 60 IV d1	
FE(50)C (27)	8 × 21 days	600 IV d1		600 IV d1	Epi 50 IV d1	
E(100)C (25)	8 × 21 days	830 IV d1			Epi 100 IV d1	
Second generation						
FAC (64)	6 × 21 days	500 IV d1		500 IV d1	Doxo 50 IV d1	
CAF-oral (65)	6 × 28 days	100 PO d1-14		500 IV d1,8	Doxo 30 IV d1,8	
FE(100)C (66)	6 × 21 days	500 IV d1		500 IV d1	Epi 100 IV d1	
CEF-oral (30)	6 × 28 days	75 PO d1-14		500 IV d1,8	Epi 60 IV d1,8	
AC-T (35, 36, 41)	AC × 4 (21 days), then Pacli	600 IV d1			Doxo 60 IV d1	Pacli[a] −175 IV Q3wks, OR −80 IV Qwk x 12
AC-D (41)	AC × 4 (21 days), then doce	600 IV d1			Doxo 60 IV d1	Doce −100 Q3wks ×4 [b] OR 35 IV Qwk × 12
TC[c] (42)	4 × 21 days	600 IV d1				Doce 75 IV d1
E-CMF (31)	E × 4, then CMF × 4 (all 21 days)	750 IV d1,8	50 IV d1	600 IV d1,8	Epi 100 d1	
Third generation						
Dose-dense AC-T[b] (40)	AC × 4, then T × 4 (all 14 days)	600 IV d1			Doxo 60 IV d1	Pacli 175 IV d1
TAC[b] (38)	6 × 21 days	500 IV d1			Doxo 50 IV d1	Doce 75 IV d1
FE(100)C ≥ D (39)	FEC × 3, then D × 3 (all 21 days)	500 IV d1		500 IV d1	Epi 100 IV d1	Doce 100 d1[b]

Carbo carboplatin; *Ctx* cyclophosphamide; *Doce* docetaxel; *Doxo* doxorubicin; *Epi* epirubicin; *5-FU* 5-fluorouracil; *H* Herceptin®/trastuzumab; *Pacli* paclitaxel

[a] Secondary analysis of INT 9741 favors paclitaxel weekly and docetaxel every 3 weeks

[b] Requires growth factor support

[c] Regimen of choice if a nonanthracycline regimen chosen

Table 61.2 Adjuvant trastuzumab-containing regimens

Regimen	Number of cycles and duration	Individual drug components, route of admin. dose in mg/m²				
		Ctx	–	Anthracycline	Taxane	Trastuzumab
AC-TH (52)	AC × 4, then TH × 4 (all 21 days except H-Qwk)	600 IV d1		Doxo 60 IV d1	Pacli 175 IV d1	Weekly × 1 year starting with pacli
AC-DH (43)	AC × 4, then DH × 4 (all 21 days except H-Qwk during chemo)	600 IV d1		Doxo 60 IV d1	Doce 100 IV d1	Weekly starting with doce, then Q21d × 1 year total
DH-FEC (55)	DH × 3, then FEC × 3 (all 21 days except H-Qwk)		5-FU 600 IV d1	Epi 60 IV d1	Doce 100 IV d1	Weekly × 9 week with doce then stopped
TCH (43)	6 × 21 days (except H-Qwk during chemo)		Carbo AUC 6 d1		Doce 75 IV d1	Weekly during chemo and then Q21d × 1 year total
Chemo of choice-H (67)						Weekly or Q3wk × 1 year after chemo

In practice, trastuzumab routinely used both weekly (4 mg/m² loading, then 2 mg/m² Qwk) and every 3 weeks (8 mg/m² loading, 6 mg/m² Q3wks)

Carbo carboplatin; *Ctx* cyclophosphamide; *Doce* docetaxel; *Doxo* doxorubicin; *Epi* epirubicin; *5-FU* 5-fluorouracil; *H* Herceptin®/trastuzumab; *Pacli* paclitaxel

Special Problems and the Triple-Negative Patient

Triple-negative (ER-, PR-, HER-2/neu) breast cancer appears to be most aggressive. A retrospective cohort of 1,601 patients at Women's College Hospital in Toronto revealed a hazard ratio of 2.6 ($p<0.0001$) and 3.2 ($p<0.001$) for distant recurrence and death within 5 years of primary diagnosis (60). The increased risk appears to be transient, however, with peak of recurrence at 3 years and rapidly declining thereafter. This population appears to be relatively resistant to chemotherapy and further trials are necessary to identify optimal chemotherapy for these women. Platinum containing regimens and Poly (ADP-Ribose) Polymerase (PARP) inhibitors are being tested in this respect. Other special problems in breast cancer include systemic therapy in pregnancy and in the elderly, which are covered in subsequent chapters. Inflammatory breast cancer also deserves special attention and is covered in the chapter on neoadjuvant chemotherapy.

Future Directions

Systemic chemotherapy research will continue to focus on identifying optimal regimens of cytotoxic chemotherapy, hormonal therapy, and incorporating targeted agents. We need to further identify which patients will benefit from anthracyclines and/or taxanes. More agents active in breast cancer need to be brought into the adjuvant setting. One such example is lapatinib, a small molecule tyrosine kinase inhibitor of the HER-2/neu receptor, which is currently being studied in phase III trials (61, 62). Further advances in molecular biology and prognostic aids will hopefully allow the practitioner to tailor treatment for each woman with breast cancer (63).

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