Substantial progress has been made in the multidisciplinary management of primary breast cancer during the last 30 years. Adjuvant chemotherapy has been shown to significantly reduce the annual risk of cancer recurrence and mortality, and these effects persist even 15 years after diagnosis. Combination chemotherapy is superior to single-agent therapy and anthracycline-containing regimens. Those that combine an anthracycline with 5-fluorouracil and cyclophosphamide are more effective than regimens without an anthracycline. Six cycles of a single regimen appear to provide optimal benefit. Dose reductions below the standard range are associated with inferior results. Dose increases that require growth factor or hematopoietic stem cell support are under investigation; at this time, the existing results provide no compelling reason to use this strategy outside a clinical trial. Regimens using fixed crossover designs with two non-cross-resistant regimens are being evaluated. The addition of a taxane to anthracycline-containing regimens is currently under intense scrutiny, and preliminary analysis of the first three clinical trials has shown encouraging, albeit not compelling, results. For patients with estrogen receptor-positive breast cancer, the sequential administration of chemotherapy and 5 years of tamoxifen therapy provides additive benefits. No compelling evidence exists to combine ovarian ablation with chemotherapy. Most side effects and toxic effects are self-limited, although premature menopause requires monitoring and preventive interventions to preserve bone mineral density. The small risk of acute leukemia is of concern, and additional research to develop safer regimens is clearly indicated. The overall effect of optimal local/regional treatment combined with an anthracycline-containing adjuvant chemotherapy and a taxane (and, for patients with estrogen receptor-positive tumors, 5 years of tamoxifen therapy) is a greater than 50% reduction in annual risks of recurrence of and death from breast cancer. For most patients at intermediate or high risk of cancer recurrence, the benefits of adjuvant chemotherapy exceed by far its unwanted effects. [J Natl Cancer Inst Monogr 2001;30:72–9]

During the last three decades of the twentieth century, substantial progress has been made in our understanding of the biology and natural history of primary breast cancer. Conceptual progress has led to improvements in the diagnosis, prevention, and treatment of breast cancer. The major tool used to validate improvements in treatment is the randomized clinical trial. Tens of thousands of women and thousands of clinical investigators have contributed to trials that have defined what should represent today's standard of care. The success of screening mammography has been reviewed elsewhere (1,2), and the development of adjuvant hormonal therapy is covered elsewhere in this Monograph (3,4). In this overview, we will summarize the evolution and current status of adjuvant chemotherapy for primary breast cancer.

BACKGROUND

A century of treatment with various forms of total mastectomy and axillary dissection (i.e., Halsted radical, Patéy modified radical, extended radical, extended simple, and total mastectomy with axillary dissection) demonstrated that early invasive breast cancer without distant metastases is curable in some patients. However, many patients developed recurrent or metastatic breast cancer despite local treatment with curative intent. Conceptual constructs and experimental data led to the hypothesis that most primary breast cancers are (or become) systemic in nature by the time the diagnosis is made; consequently, regional therapies cannot provide a realistic probability of cure once micrometastatic deposits have been established. The concept of “adjuvant” chemotherapy was first introduced in the 1950s (5,6) to combine optimal local/regional and systemic treatments and, thus, to maximize the probability of cure. The first test of this strategy was the administration of thiotepa or 5-fluorouracil to patients with operable breast cancer during radical mastectomy and each of the 2 following days. Patients receiving thiotepa or 5-fluorouracil were compared with those receiving placebo (5). A transient delay in cancer recurrence was documented in the premenopausal group receiving chemotherapy. Subsequent clinical trials (7–9) established clearly that adjuvant chemotherapy reduced statistically significantly the annual odds of cancer recurrence and death. The Early Breast Cancer Trialists’ Collaborative Group (10–13) performed overviews of all randomized clinical trials testing adjuvant chemotherapy and confirmed and extended the observations from individual clinical trials. We will review the existing data in the context of specific and clinically relevant questions.

WHAT IS THE BENEFIT OBTAINED WITH ADJUVANT CHEMOTHERAPY?

The evidence is overwhelming that adjuvant chemotherapy produces a highly statistically significant reduction in the annual odds of cancer recurrence and death (10–13). This significant reduction is observed in all subgroups in which the hypothesis has been adequately tested. Thus, the relative reduction in the odds of cancer recurrence and death is similar in patients with lymph node-negative and lymph node-positive breast cancer. The absolute clinical benefit depends, however, on the initial risk of cancer recurrence and death (Table 1).

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See “Note” following “References.”

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IS THE BENEFIT FROM ADJUVANT CHEMOTHERAPY MODIFIED BY PATIENT OR TUMOR CHARACTERISTICS?

Chemotherapy appears to be more effective for women younger than age 50 years than for women older than age 50 years. Although this is the message clearly given by an overview of the world’s randomized trials (13), it is not universally confirmed by individual large randomized studies (14,15). Concerns persist about the adequacy of doses delivered to postmenopausal women (as compared with premenopausal women). In many of the earlier studies of adjuvant chemotherapy doses lower than the standard have been associated with inferior results (15–17). Conversely, there are biologic bases for a potentially greater benefit from adjuvant chemotherapy in premenopausal women. Most chemotherapy regimens used in the adjuvant setting contain an alkylating agent. These drugs produce permanent amenorrhea (i.e., premature menopause) in more than two thirds of younger patients. Therefore, chemotherapy has both a cytotoxic and an endocrine effect in premenopausal women. The effect of adjuvant chemotherapy in women older than age 70 years has not been adequately tested. An important area for research is the state-of-the-art chemotherapy regimens used to treat women older than age 70 years—a thorough evaluation of these treatment plans and their effects is needed.

Another factor that modifies the effect of adjuvant chemotherapy is the estrogen receptor status of the tumor. The reduction in odds of cancer recurrence or death is 30%–40% greater for estrogen receptor-negative primary tumors than for estrogen receptor-rich tumors (13,20). These differences are observed in both younger and older patient groups.

Preliminary data based on retrospective analyses of clinical trials suggest that anthracycline-containing chemotherapy regimens might be particularly effective in treating HER-2-overexpressing tumors. Additional information about this potential interaction will be needed, preferably from prospective trials.

Combination chemotherapy is significantly more effective than single-agent chemotherapy, both in individual clinical trials and in the world overview (13,20–22). Whether the most effective drugs should be combined simultaneously or in sequence is currently under evaluation. Until those studies are completed, the standard of care is to use simultaneous combinations, as is detailed below.

WHAT IS THE OPTIMAL DURATION OF ADJUVANT CHEMOTHERAPY?

The first studies of adjuvant chemotherapy (5,23–25) used a short course of perioperative chemotherapy only. The effects of these interventions were marginal. The demonstration of substantial and reproducible benefit from prolonged combination chemotherapy as well as the greater benefit derived from longer therapy established this latter strategy as the standard of care (8,9). Several randomized clinical trials (13,26–31) addressed this specific issue. The results of these trials can be summarized as follows: The use of a single-combination chemotherapy regimen for longer than 6 months is not more beneficial than 6 months of treatment (13,27–29). Regimens that use chemotherapy for less than 3–4 months appear to be inferior in efficacy (30,31). Therefore, with regimens currently in use (e.g., cyclophosphamide/methotrexate/5-fluorouracil [CMF], cyclophosphamide/doxorubicin/5-fluorouracil [CAF or FAC], or similar epirubicin-containing combinations [CEF or FEC]), six cycles of therapy administered over a 4- to 6-month period appear to be an optimal regimen. In fact, the adequacy of four cycles of doxorubicin/cyclophosphamide should be questioned. Newer regimens that use two different non-cross-resistant regimens may require eight cycles over a 6-month period or a longer period (32–35).

WHAT IS THE OPTIMAL TIMING OF THE INITIATION OF ADJUVANT CHEMOTHERAPY?

Preclinical experiments suggest that the earlier the initiation of chemotherapy in relation to the injection of tumor cells or the resection of the primary lesion, the higher the cure rate (36–38). Clinical trials have not been designed to determine the efficacy of delayed adjuvant chemotherapy. Therefore, virtually all of the data that we have relevant to this question are derived from trials in which eligibility required starting adjuvant chemotherapy within 60 days of the primary surgical procedure. Within this narrow window, there is no evidence that chemotherapy initiated earlier is more beneficial than chemotherapy initiated later. However, a few retrospective analyses (39,40) have suggested that, for high-risk patients, delaying initiation of chemotherapy might be detrimental. Furthermore, a prospective randomized trial comparing postoperative chemotherapy followed by radiotherapy with the reverse sequence of treatment indicated that delaying chemotherapy until the completion of radiotherapy was associated with increased rates of distant metastases and death.

### Table 1. Relative and absolute reductions in annual odds of recurrence after adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Disease-free survival after</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>90%</td>
<td>81%</td>
<td>72.9%</td>
<td>65.61%</td>
<td>59.05%</td>
</tr>
<tr>
<td>Relative reduction with chemotherapy</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>93.5%</td>
<td>87.42%</td>
<td>81.74%</td>
<td>76.43%</td>
<td>71.46%</td>
</tr>
<tr>
<td>Absolute reduction</td>
<td>5.5%</td>
<td>6.42%</td>
<td>8.84%</td>
<td>10.82%</td>
<td>12.41%</td>
</tr>
</tbody>
</table>

A) Benefit over a 5-y period, assuming a relative reduction in odds of recurrence of 35% and a baseline risk of recurrence of 10%/y

B) Benefit over a 5-y period, assuming a relative reduction in odds of recurrence of 35% and a baseline risk of recurrence of 5%/y

| Surgery                     | 95%  | 90.25%| 85.74%| 81.45%| 77.38%|
| Relative reduction with chemotherapy | 35%  | 35%  | 35%  | 35%  | 35%  |
| Surgery + chemotherapy      | 96.75%| 93.61%| 90.57%| 87.63%| 84.78%|
| Absolute reduction           | 1.75%| 3.36% | 4.83%| 6.18% | 7.40% |
On the basis of this limited information, postoperative adjuvant chemotherapy should begin as soon as possible after the surgical procedure and should precede radiotherapy, especially in patients at high risk of recurrence or metastases.

A question regarding the timing of systemic therapy is whether chemotherapy should start even before definitive surgery. Preoperative chemotherapy has several potential advantages, including reduction in tumor volume, facilitation of breast-conserving therapies, and the opportunity it provides to evaluate chemotherapy sensitivity in vivo (42, 43). Several randomized clinical trials (44–47) have compared the administration of chemotherapy before or after definitive surgical procedures. The largest of these was the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18 (44, 45). All trials reported to date have shown that preoperative chemotherapy produced results that were virtually identical to those obtained with the postoperative administration of the same regimen. In two smaller trials (46, 47), a small advantage was associated with preoperative therapy. Although the optimal utilization of preoperative adjuvant chemotherapy is still under investigation, this appears to be a safe and effective alternative to surgery followed by chemotherapy, especially for primary tumors that would require cytotoxic treatment anyway.

**WHAT IS THE ROLE OF ANTHRACYCLINES IN THE ADJUVANT THERAPY OF BREAST CANCER?**

Until recently, anthracyclines were considered to be the most effective agents for the treatment of metastatic breast cancer. On the basis of randomized trials (13, 48, 49), it is evident that anthracycline-containing regimens produce higher response rates and longer response durations and survival than regimens that lack an anthracycline. For this reason, anthracyclines were introduced into adjuvant chemotherapy regimens (9, 50–57). The adoption of anthracycline-containing adjuvant regimens has been slow, however, because of concerns about cardiotoxicity (58). Although long-term cardiotoxic effects have been described in the pediatric literature, the risk of late cardiotoxic effects remains very low in the adult population, with cumulative doses of doxorubicin or epirubicin limited to well below the cardiotoxic threshold (56, 57, 59–62). In the metastatic setting, the risk of cardiac toxicity can be reduced by limiting the cumulative dose of the anthracycline (58), by using 48- to 96-hour continuous infusion schedules (63), or by using a cardioprotector (dexrazoxane) (64, 65) or an anthracycline with lower cardiotoxic potential [such as epirubicin (66), liposomal doxorubicin (67), or stealth liposomal doxorubicin (68)]. In addition to long-term safety data from a few trials with follow-up periods exceeding 10 years (69, 70), there are now more than 15 reported prospective randomized trials of adjuvant chemotherapy regimens that include an anthracycline (52, 54–56, 71–79). Several individual trials (52, 55, 57) and the world overview (12, 13, 20) of all randomized trials have demonstrated that anthracycline-containing chemotherapy regimens are associated with higher disease-free and overall survival rates than regimens that do not include anthracyclines. The annual reduction in odds of recurrence was 12% [standard deviation (SD), 4%]; the reduction in odds of death was 11% [SD, 5% (13)]. However, the clinical trials on which this calculation was based included a variety of anthracycline-containing chemotherapy regimens, some of them considered to be, in retrospect, suboptimal. The first two NSABP protocols that incorporated doxorubicin utilized this drug at 30 mg/m² every 28 days (52). This dose (or dose intensity) is known to be less effective than more commonly used dose regimens (17). Furthermore, in several trials (54, 75, 77, 78), the two drug (doxorubicin/cyclophosphamide [AC] or epirubicin/cyclophosphamide [EC]) combination was used as the “investigational” arm; this regimen was shown in a large trial (54) to be equivalent to but not better than the CMF combination (54, 75, 77–79). Neither AC nor EC has ever been directly compared with the more standard three-drug regimens (FAC/CAF or FEC/CEF) that have been shown to produce superior disease-free or overall survival rates when compared with CMF (Table 2). These indirect comparisons between AC and FAC (or the epirubicin equivalents) invite the question of whether AC is equivalent to or inferior to FAC. In the absence of direct comparisons between AC and FAC, prudence dictates that FAC (or CAF, FEC, or CEF) rather than AC be considered the standard anthracycline-based regimen. Whether the apparent superiority of FAC/CAF over AC results from the use of a third drug, 5-fluorouracil, or the longer duration of therapy (usually six to eight cycles of FAC/FEC versus four cycles of AC/EC) is unknown. The determination of the optimal duration of therapy and the optimal number of drugs in anthracycline-containing regimens is an important research question as the choice of the “standard arm” of subsequent trials depends on this answer. Were the results in the taxane arm of Cancer and Leukemia Group B (CALGB) 9344 (32) better than the results for those who received four cycles of AC because a longer duration of therapy was used or because paclitaxel was substituted for 5-fluorouracil?

The recent update of the Scandinavian trial comparing a tailored FEC regimen with four cycles of FEC followed by one cycle of high-dose chemotherapy indicated the superiority of the tailored FEC regimen (80). Should this regimen be the next standard of care and, therefore, the gold standard in future clinical trials?

Additional important research questions remain to be answered concerning the role of other anthracyclines [liposomal anthracyclines (67, 68, 81) or anthrapyrazoles (82)] in the adjuvant chemotherapy setting.

**WHAT IS THE ROLE OF TAXANES IN ADJUVANT CHEMOTHERAPY?**

The two commercially available taxanes, paclitaxel and docetaxel, are considered the most effective agents against metastatic breast cancer (83–86). Their efficacy matches, and in some cases exceeds, that of the anthracyclines. Both taxanes have been shown to increase response rates and to prolong response duration and overall survival in some randomized trials (87–91). Therefore, the introduction of taxanes into adjuvant chemotherapy regimens was a logical step. To date, the preliminary results of three randomized trials that evaluated the inclusion of a taxane into adjuvant therapy have been presented (Mamounas EP: Results of National Surgical Adjuvant Breast and Bowel Project protocol B-28, presented at the National Institutes of Health Consensus Development Conference on Adjuvant Therapy for Breast Cancer, Oct. 31–Nov. 3, 2001, Bethesda, MD) (32, 92). In essence, the addition of four cycles of paclitaxel to four cycles of AC significantly reduced the annual odds of cancer recurrence and death (32). On the basis of these results, the U.S. Food and Drug Administration approved the use of paclitaxel in the adjuvant chemotherapy setting. The preliminary re-
appears to be superior to CMF2 (the dose schedule used in the second half of the study by Coombes) in disease-free survival rate and overall survival rate. FEC2 (the dose schedule used in the second half of the study by Coombes)

<table>
<thead>
<tr>
<th>Author (study)</th>
<th>No. of patients: A/non-A</th>
<th>Regimens†</th>
<th>Year</th>
<th>Lymph node-positive</th>
<th>Median follow-up, mo</th>
<th>Disease-free survival rate</th>
<th>Overall survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchins (55)</td>
<td>1340/1351</td>
<td>CAFCMF</td>
<td>1998</td>
<td>None</td>
<td>84</td>
<td>85</td>
<td>82±</td>
</tr>
<tr>
<td>Mouridsen (76)</td>
<td>1195</td>
<td>CEFCMF</td>
<td>1999</td>
<td>None</td>
<td>61</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fisher (B12) (52)</td>
<td>548/558</td>
<td>PAFT/PFT</td>
<td>1989</td>
<td>All</td>
<td>64</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Fisher (B11) (52)</td>
<td>347/360</td>
<td>PAF/PF</td>
<td>1989</td>
<td>All</td>
<td>51</td>
<td>51</td>
<td>44‡</td>
</tr>
<tr>
<td>Levine (MA5) (73)</td>
<td>351/359</td>
<td>CEFCMF</td>
<td>1998</td>
<td>All</td>
<td>60</td>
<td>63</td>
<td>53‡</td>
</tr>
<tr>
<td>Carpenter (71)</td>
<td>260/268</td>
<td>CAFCMF</td>
<td>1991</td>
<td>All</td>
<td>42</td>
<td>NA</td>
<td>NA§</td>
</tr>
<tr>
<td>Coombes (72)</td>
<td>380/379</td>
<td>FEC/CMF</td>
<td>1996</td>
<td>All</td>
<td>54</td>
<td>NA§</td>
<td>NA§</td>
</tr>
</tbody>
</table>

AC or EC vs. CMF

<table>
<thead>
<tr>
<th>Author (study)</th>
<th>No. of patients: A/non-A</th>
<th>Regimens†</th>
<th>Year</th>
<th>Lymph node-positive</th>
<th>Median follow-up, mo</th>
<th>Disease-free survival rate</th>
<th>Overall survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher (B23) (78)</td>
<td>1003/1005</td>
<td>AC/CMF</td>
<td>2000</td>
<td>None</td>
<td>67</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Fisher (B15) (54)</td>
<td>781/776</td>
<td>AC/CMF</td>
<td>1990</td>
<td>All</td>
<td>26</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Di Leo (73)</td>
<td>562/255</td>
<td>EC/CMF</td>
<td>1999</td>
<td>All</td>
<td>50</td>
<td>64-74</td>
<td>71</td>
</tr>
<tr>
<td>Galliottini (77)</td>
<td>103/104</td>
<td>EC/CMF</td>
<td>1997</td>
<td>All</td>
<td>36</td>
<td>72</td>
<td>63</td>
</tr>
</tbody>
</table>

†FAC = 5-fluorouracil, doxorubicin (i.e., Adriamycin), and cyclophosphamide; CAFCMF = cyclophosphamide, doxorubicin, and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; PAF = L-phenylalanine mustard, doxorubicin, and 5-fluorouracil; T = tamoxifen; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; NA = not available.

§Separate sets of numbers given for different schedules of FEC and CMF. FEC1 (the dose schedule used in the first half of the study by Coombes) and CMF1 (the dose schedule used in the first half of the study by Coombes) appear equivalent. FEC2 (the dose schedule used in the second half of the study by Coombes) appears to be superior to CMF2 (the dose schedule used in the second half of the study by Coombes) in disease-free survival rate and overall survival rate.

**Table 2.** Randomized trials comparing anthracycline-containing with non-anthracycline-containing combination chemotherapy regimens as adjuvant therapy for operable breast cancer

- A = anthracycline-containing regimen; ER = estrogen receptor.
- FAC = 5-fluorouracil, doxorubicin (i.e., Adriamycin), and cyclophosphamide; CAF = cyclophosphamide, doxorubicin, and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; PAF = L-phenylalanine mustard, doxorubicin, and 5-fluorouracil; T = tamoxifen; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; NA = not available.
- Statistically significant difference (two-sided P<.05).
- Separate sets of numbers given for different schedules of FEC and CMF. FEC1 (the dose schedule used in the first half of the study by Coombes) and CMF1 (the dose schedule used in the first half of the study by Coombes) appear equivalent. FEC2 (the dose schedule used in the second half of the study by Coombes) appears to be superior to CMF2 (the dose schedule used in the second half of the study by Coombes) in disease-free survival rate and overall survival rate.

The answer to this question is, certainly, yes; however, it is a highly qualified yes. Extensive data from preclinical experiments show a direct correlation between dose and extent of cytotoxicity (93); however, there are only a few well-designed clinical trials to address the issue of dose. In both the metastatic and the adjuvant setting, there are data to show that variations in dose or dose intensity are important. It is unclear from published studies whether dose, dose intensity, or dose density is the most influential factor. However, the data can be interpreted to show that reductions in dose below the optimal dose possible without hematopoietic stem cell and growth factor support. Preliminary analyses in two of the trials (96,97) suggested a decrease in the number of recurrences in the group receiving the high-dose therapy, whereas there was no detectable difference in the other three studies. Several additional randomized trials addressing this important question are still in the patient-recruitment phase (98). Mature results of all these completed and ongoing trials will determine whether high-dose chemotherapy has a role in the management of patients with high-risk primary breast cancer. At the moment, there is no indication that high-dose chemotherapy should be used outside a well-designed clinical trial.

**IS THE DOSE OF CHEMOTHERAPY AN IMPORTANT DETERMINANT OF OUTCOME AFTER ADJUVANT CHEMOTHERAPY?**

The answer to this question is, certainly, yes; however, it is a highly qualified yes. Extensive data from preclinical experiments show a direct correlation between dose and extent of cytotoxicity (93); however, there are only a few well-designed clinical trials to address the issue of dose. In both the metastatic and the adjuvant setting, there are data to show that variations in dose or dose intensity are important. It is unclear from published studies whether dose, dose intensity, or dose density is the most influential factor. However, the data can be interpreted to show that reductions in dose below the optimal dose possible without hematopoietic stem cell and growth factor support result in decreased benefit (17). These studies are consistent with the existence of a dose threshold below which the treatment loses its effectiveness. Therefore, recommended doses for commonly used regimens should not be altered unless the patient’s safety requires it. Retrospective subset analyses suggest that dose reductions would have an adverse effect for HER-2-positive but not for HER-2-negative tumors. Above the standard dose range, existing data are inconclusive. Five prospective randomized trials (80,94–97) have been reported to date that compare a “standard dose” regimen with a high-dose regimen. All five trials required hematopoietic stem cell and growth factor support. Preliminary analyses in two of the trials (96,97) suggested a decrease in the number of recurrences in the group receiving the high-dose therapy, whereas there was no detectable difference in the other three studies. Several additional randomized trials addressing this important question are still in the patient-recruitment phase (98). Mature results of all these completed and ongoing trials will determine whether high-dose chemotherapy has a role in the management of patients with high-risk primary breast cancer. At the moment, there is no indication that high-dose chemotherapy should be used outside a well-designed clinical trial.

**DOES THE COMBINATION OF ADJUVANT CHEMOTHERAPY AND HORMONE THERAPY PRODUCE SUPERIOR RESULTS TO CHEMOTHERAPY ALONE OR TO HORMONE THERAPY ALONE?**

This question is restricted to patients with hormone receptor-positive breast cancer, since hormone therapy produces no benefit in women with hormone receptor-negative tumors (3). Several randomized trials have addressed this issue in women with hormone receptor-positive (or unknown) breast cancer. The last two world overviews have also analyzed the pooled data from these trials (13). The addition of tamoxifen therapy to adjuvant chemotherapy statistically significantly increases the disease-free and overall survival rates of patients with hormone receptor-positive tumors. This effect is observed regardless of age or lymph node status and appears to be of the same magnitude in both younger women and older women. Conversely, the addition of chemotherapy to tamoxifen therapy statistically significantly increases the results of treatment compared with tamoxifen therapy alone. Therefore, for women with hormone receptor-positive breast cancer, the treatment of choice is the combination of chemotherapy and 5 years of tamoxifen therapy. Most on-
The combination of chemotherapy with ovarian ablation is currently under intense scrutiny in several randomized trials (101). This topic is reviewed in detail elsewhere in this Monograph (4). At this time, there is no compelling evidence to support the combination of any form of ovarian ablation with chemotherapy. Instead, tamoxifen therapy combined with chemotherapy appears to be the treatment of choice. No information is available about the role of aromatase inhibitors or other endocrine interventions in the adjuvant chemotherapy setting, although the former are currently under investigation in clinical trials.

**WHAT IS THE OVERALL BENEFIT OF ADJUVANT SYSTEMIC THERAPY?**

Many physicians and patients assume that the results of individual trials comparing two closely related treatments or similar analyses from the world overview (12) represent the best that adjuvant systemic therapy has to offer. In reality, progress is stepwise and incremental. Thus, it is important to combine the effects of all incremental steps to determine the overall impact of combined-modality therapy for primary breast cancer. We do not know the overall impact of optimal surgical resection on disease-free and overall survival, since this has never been (and perhaps will never be) the subject of randomized trials. However, we have ample evidence that the addition of postoperative radiation therapy to surgery statistically significantly reduces the risk of recurrence and mortality from breast cancer (102). Furthermore, we have compelling evidence that first-generation chemotherapy regimens (CMF and related combinations) reduce annual odds of cancer recurrence by 23% (SD, 2.1) and odds of death by 15% (SD, 2.4) (13). The addition of an anthracycline further reduces residual risk by 12% and 11%, respectively. These latter figures probably represent an underestimate, based on the caveats expressed in the anthracycline section of this article. On the basis of the results of CALGB 9344, it is probable that adding a taxane to an anthracycline-based regimen will produce an additional reduction in risk of cancer recurrence and mortality. Finally, there is compelling evidence that the combination of 5 years of tamoxifen therapy with chemotherapy results in statistically significant improvements to outcome (3). Therefore, if one uses optimal surgical therapy, radiotherapy, state-of-the-art chemotherapy, and, for hormone receptor-positive tumors, tamoxifen therapy, the overall reduction in risk of cancer recurrence will probably exceed 50%, and the reduction in mortality should also approach that figure. Although individual patients might want to look at the contribution of each component of their treatment, it is helpful to point out the overall benefits obtained with the entire treatment strategy relevant to that patient and her tumor.

**WHAT ARE THE SIDE EFFECTS AND THE SHORT-TERM AND LONG-TERM TOXIC EFFECTS OF ADJUVANT SYSTEMIC CHEMOTHERAPY?**

This is a critical component of the therapeutic ratio and is reviewed in detail by Dr. Winer's article (103). Most chemotherapy regimens in use today have the potential to produce nausea, vomiting, mucositis, diarrhea, and alopecia in different degrees (60). All of these effects are self-limited, and we have effective tools to modify or prevent their occurrence. Myelosuppression is common, but neutropenic febrile episodes are uncommon and frank infections are rare. Deaths from toxicity should be exceptional when average-risk patients receive therapy from expert hands. Premature menopause is the most common long-term toxicity for premenopausal women (60, 104). Emerging data suggest that this might be a desirable effect of chemotherapy, which is associated with improved outcomes. Menopausal symptoms can be successfully controlled with medical interventions in a high proportion of patients, while the long-term effects of premature menopause on cardiovascular risk and the early onset of osteoporosis can be successfully managed with statins and bisphosphonates or selective estrogen receptor modulators, respectively.

The development of myelodysplastic syndromes or acute leukemia is a known (albeit rare) complication of chemotherapy with alkylating agents and topoisomerase II inhibitors (105–107). The cumulative incidence of these disorders is around 1% for commonly employed regimens. These events are, however, life threatening, so the development of even safer chemotherapy regimens or the identification of patients at greater than average risk for these complications should be a high priority of research in the near future.

**SELECTION OF OPTIMAL ADJUVANT SYSTEMIC THERAPY**

Because of our improved ability to reduce the risk of recurrence and, especially, of death, most patients with primary invasive breast cancer should receive multidisciplinary treatments. Thus, it is accepted practice that all patients with a calculated risk of recurrence exceeding 10% over a 10-year period should be advised to receive adjuvant systemic therapy. Most otherwise healthy patients with a calculated risk between 5% and 10% should have their available treatment options discussed with them; many will choose to receive hormone therapy, chemotherapy, or a combination of both. Once a decision has been made about the need for or desirability of adjuvant systemic therapies, the following guidelines should be considered:

1. **All patients with hormone receptor-positive tumors should receive tamoxifen therapy for 5 years.** Patients with hormone receptor-negative tumors should not be offered adjuvant hormone therapies.

2. **The treatment of choice for patients with hormone receptor-negative tumors is combination chemotherapy, preferably with an anthracycline-containing regimen.** The three-drug regimens (FAC, CAF, FEC, or CEF) are preferred to AC or EC. Six cycles of therapy with a single regimen is probably optimal.

3. **The addition of taxanes should be considered for high-risk patients with lymph node-positive breast cancer, especially if the cancer is hormone receptor negative.**

4. **For most patients at intermediate or high risk of recurrence and of death and with hormone receptor-positive tumors, the sequential combination of chemotherapy and tamoxifen therapy for 5 years represents the treatment of choice.**

5. **The use of optimally performed interventions provides maximal benefits.** Chemotherapy is no substitute for good surgery, or vice versa.
6) The combined use of optimal surgery, chemotherapy, tamoxifen therapy, and radiotherapy has a major impact on the risk of recurrence and death.

REFERENCES


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