Controversial Issues in Adjuvant Systemic Therapy of Early Breast Cancer

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Although it has been shown that adequate local therapy of primary breast cancer decreases the risk of distant failure and death due to the disease, treatment results with local therapy alone are clearly inadequate with c. 30–40% of patients developing a disease recurrence within the first ten years after primary diagnosis. In the past 10–15 years there has been significant progress in the field of systemic adjuvant therapy of breast cancer. It is now reliably established that the concept is valid; that is, that early treatment with either cytotoxic chemotherapy or endocrine therapy does result in improved survival compared with treatment deferred until relapse. Despite considerable progress, several controversial issues remain. These include the optimal timing and sequencing of treatment, optimal drug doses, and the role of new drugs such as taxanes and new endocrine agents. The identification of more powerful prognostic and/or predictive tests might have substantial clinical implications but major breakthroughs in this field of research are still to come. A relatively new and important issue in clinical decision-making regarding the use of different adjuvant therapies is long-term toxicity such as leukemia with some types of chemotherapy and endometrial cancer (and possibly other malignancies) with long-term tamoxifen. Further progress in the field of adjuvant therapy of breast cancer continues to rely on well-designed, prospective, controlled clinical trials and overviews of such studies.

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During the first 10 years after primary diagnosis c. 30–40% of women with early-stage breast cancer will develop a distant disease recurrence. Although it has been shown that adequate local therapy that decreases the risk of local failure may also decrease the risk of distant metastases and death due to the disease (1, 2), treatment results with local therapy alone are clearly inadequate. According to scientific hypotheses established for experimental tumors, systemic treatment should be the most effective when the tumor burden is low. Prophylactic ('adjuvant') therapy given in conjunction with the primary treatment should therefore be more effective than treatment deferred until relapse. Furthermore, putatively more effective regimens, for instance prolonged multi-drug combinations as opposed to short-term single agents, and increased dose intensity should also be more effective. These and other hypotheses concerning adjuvant systemic therapy of early-stage breast cancer have been tested in a large number of controlled clinical trials during the past decades. The first of these trials was actually initiated in 1948. Despite considerable progress over the past 50 years several controversial issues remain.

CONTROLLED CLINICAL TRIALS

The natural time history of breast cancer is highly variable. Accurate prediction of the outcome for individual patients is difficult despite recent advances in our understanding of breast cancer biology and the plethora of prognostic factors. These problems are the main rationale for evaluating treatment outcome using the method of the controlled clinical trial. Such trials are probably unnecessary to identify treatments associated with large survival benefits, but represent the currently only method to detect small to moderate improvements. The available studies of high-dose chemotherapy and autologous bone marrow transplantation illustrate this problem. Almost all of these studies have been non-randomized. Claims of efficacy have mainly been based on comparisons with historical control groups. However, patients included in these studies may represent a select group of patients. For instance, many of them were offered high-dose treatment because they had responded to induction chemotherapy. Such patients may fare relatively well even with conventional regimens (3). So, historical controls are clearly inadequate and may lead to erroneous conclusions.

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Table 1

Survival benefit with adjuvant systemic therapy. Results adapted from the 10-year update of the overview of adjuvant systemic therapy trials (6)

Benefit, subgroup	Type of therapy, age group: Ovarian ablation <50 years	Adjuvant TAM	Adjuvant CT <50 years	Adjuvant CT 50–70 years
Relative reduction of deaths:	24%	23%	25%	12%
Absolute 10-year survival increase:				
Node-positive	10%	10%	10%	5%
Node-negative, 'high risk'	8%	8%	8%	4%
Node-negative, 'low risk'	2%	2%	2%	1%

OVERVIEWS

To come to a reliable assessment of the effects of moderate treatment, it must be possible to exclude moderate biases and moderate random errors as explanations for observed differences in treatment outcome. This might be difficult or even impossible in individual trials with several hundreds of patients. In such a setting the play of chance may produce random errors that are comparable in size to moderate treatment effects that are potentially clinically worthwhile. Over the years it has become increasingly clear that breast cancer adjuvant trials need to include several thousands rather than several hundreds of patients in order to generate statistically reliable results. Up until 1985 more than 130 randomized trials of adjuvant systemic treatment in early-stage breast cancer were initiated including a total of more than 74000 women. These trials have been included in the international overview of breast cancer trials initiated by the Oxford group headed by Richard Peto (4–6) (Table 1). This overview also includes c. 28000 patients in almost 60 trials of local therapy including 17000 patients in 36 unconfounded radiation therapy trials.

The principal aim of an overview of trials ('meta-analysis') is to increase the number of events so that random errors in the estimates of the treatment effect are minimized. Other aims set by the Oxford group are the inclusion of only properly randomized studies, that is, studies in which the randomization technique has been such that the treatment allocation was truly random, and inclusion of all initiated studies irrespective of whether they have been published or not (to avoid 'publication bias'). In the Oxford overview a clear distinction has also been made between confounded and unconfounded study designs. In an unconfounded trial the only difference between two study arms is the intervention being studied, for instance, a trial where patients are randomly allocated between surgery plus chemotherapy and the same type of surgery without chemotherapy. A confounded design is when, for example, one type of chemotherapy is compared with another type.

It is now well accepted that the Oxford overviews have greatly contributed to our knowledge about the effect of different treatments used in the primary management of breast cancer patients. They have also clarified many controversial issues. However, there are several drawbacks with the overview methodology. One is the fact that in some cases it is impossible to judge the relevance of a particular overview result because relevant details from the trials contributing to the result are unavailable. One example is the overview of radiation therapy trials where it has been impossible to judge the relevance of treatment technique because technical details have been unavailable (7). Another drawback is the inclusion of trials using inadequate or outdated methods that are no longer relevant to current medical practice. One example is probably the lack of correlation between estrogen receptor status and effect of adjuvant tamoxifen in the early reports from the tamoxifen trial overview (4, 5). Recent updates have shown a significant correlation, at least among premenopausal women, possibly as a result of the inclusion of recent studies with more accurate receptor assays (8). Finally, yet another drawback is the possibility of confounding when a large number of heterogeneous trials contribute to a particular result. An example is the lack of a significant effect of tamoxifen in women under 50 years in the tamoxifen trial overview published in 1992 (6). A later update has confirmed a significant benefit also in this age group (8). The 1992 result was probably confounded by the inclusion of a relatively large number of young women included in trials in which tamoxifen treatment was given for only 6–12 months, a duration we now know to be associated with poorer results than more long-term treatment. Questions related to the performance of the treatment being studied, the potential significance of prognostic and predictive tests, and putative treatment interactions are perhaps more adequately addressed in individual studies than in large overviews.

CHEMOTHERAPY TRIALS

In 1975 Fisher et al. presented their first data on the efficacy of adjuvant, single-agent chemotherapy (9). In 1976 the Milan group published similar data on multi-drug chemotherapy (10). Later updates have confirmed the early, promising results with significantly better disease-free and overall survival among those allocated to chemotherapy compared to the surgical controls (11). Up

Table 2

Summary of randomized breast cancer chemotherapy trials testing the relevance of drug dose. Adapted from Savarese et al. (28)

Setting, first author	No. of pts	CT regimen, study design	Survival
Metastatic disease:			
Hortobagyi et al. (24)	59	FAC: stand. vs. intense	20 vs. 20 months (median survival)
Tannock et al. (21)	133	CMF: stand. vs. low-dose	16 vs. 13 months (median survival)
Engelsman et al. (22)	254	CMF: stand. vs. low-dose	17 vs. 12 months (median survival)
Bezwoda et al. (26)	90	High-dose CT + ABMT/PBPC	90 vs. 45 weeks vs. standard CT (median survival)
Peters et al. (27)		Initial vs. delayed high-dose CT + ABMT/PBPC (after CR with induction CT)	1.9 years vs. 3.2 years (median survival)
Adjuvant therapy:			
Wood et al. (23)	1 529	FAC: low vs. stand. vs. intense	84% vs. 90% vs. 92% (3-year OS)
Dimitrov et al. (25)	2 238	AC: stand. vs. intense vs. intense/high cumul. dose	87% vs. 89% vs. 89% (3-year OS)

Abbreviations: CT = chemotherapy; FAC = fluorouracil, adriamycin, cyclophosphamide; stand. = standard dose; CMF = cyclophosphamide, methotrexate, fluorouracil; ABMT = autologous bone marrow transplantation; PBPC = peripheral blood progenitor cells; CR = complete remission; OS = observed survival; AC = adriamycin, cyclophosphamide.

to 1985 more than 40 randomized, unconfounded, adjuvant cytotoxic chemotherapy trials were initiated with a total of more than 18000 patients. There were also 46 trials with more than 19000 patients that compared different types of chemotherapy. The Oxford chemotherapy trial overview has provided conclusive evidence that there is a definite survival benefit with adjuvant chemotherapy, that multiple drug regimens produce better results than single-agent treatment, that the benefit seems to concern all studied subgroups of patients although the benefit in absolute terms may vary, and that longer treatment periods (>12 months) in general do not seem to produce better results than shorter treatment regimens (4–6). The benefit observed at 10 years in the overview of prolonged polychemotherapy trials in relative and absolute terms in selected subgroups of patients is presented in summary in Table 2. One important observation is that adjuvant chemotherapy seems to be much less effective in women aged above 50 years than in younger patients. An open question is thus, whether some of the chemotherapy benefit in young women is mediated through endocrine mechanisms (12) or whether the difference should be attributed to variations in chemotherapy dose intensity (13). In general, older women tend to tolerate full protocol doses less well than young patients.

DESCRIPTION OF TREATMENT BENEFIT

In the overview as well as in the reports of several individual trials the benefit with adjuvant therapy is described in terms of the proportional reduction in recurrences or deaths. It is important to understand that a similar proportional reduction does not imply a similar absolute benefit. The latter depends on the baseline risk without treatment. Given the same proportional benefit, the absolute benefit is greater in a high-risk than in a low-risk population. For instance, an improvement in survival rate from 60% to 70% or from 92% to 94% implies a similar proportional benefit, that is, a mortality reduction of 25%. An absolute survival increase at a given point in time of, for instance, 60% to 70% is sometimes interpreted to imply that only one patient in ten has benefited, and that the others were treated in vain. This interpretation is probably incorrect in most cases. The problem is that in breast cancer we do not know the mechanism for the benefits observed with adjuvant therapy. Theoretically, the treatment might cure a certain proportion of patients, whereas those who are not cured derive no benefit at all. An alternative hypothesis, however, is that no patient is cured but that all patients benefit from treatment through postponement of recurrence and death. Given the long natural time history of breast cancer it is impossible to distinguish between these two hypotheses by comparing survival curves for treated and untreated patients. Even so, it seems intuitively reasonable to use absolute survival benefits to compare the relative efficacy of different treatments in a given patient population. It has been suggested that prolongation of the median survival time can be used as an alternative measure of benefit. A benefit corresponding to a persistent 25% mortality reduction in a population with a baseline survival of 50% at 5 years implies a prolongation of the median survival from 5 years to 6.7 years.

Adjuvant therapy is often associated with morbidity from the treatment. If a particular treatment is associated with a relatively modest benefit but considerable toxicity, it might not be considered 'clinically worthwhile'. Calculation and comparisons of TWIST or Q-TWIST(Quality-adjusted Time Without Symptoms or Treatment) represent an interesting method to conceptualize the mentioned intuitive principles for clinical decision-making (14). However, a practical problem associated with this approach lies in the fact that individual patients may have widely differing opinions about the extent to which toxicity from treatment or symptoms from disease recurrence affect their quality of life.

ANTHRACYCLINES

Until the introduction of taxanes, anthracyclines were the most effective drugs for metastatic breast cancer. They were introduced in adjuvant regimens in order to increase efficacy. At many centers today anthracycline-containing adjuvant regimens are used routinely. However, it remains an open question whether they, in fact, are superior to the original CMF schedule used in the first Milan trial. In the chemotherapy trial overview there were no statistically reliable data from trials directly comparing an anthracycline-containing regimen with an alternative multi-drug regimen. However, indirect comparisons, that is, comparisons of the benefit observed in one set of trials to the benefit observed in another set, suggested little, if any, difference between the relative reduction in the odds of recurrence achieved in the CMF trials (32%) versus trials using other multiple-agent cytotoxic regimens including those with anthracyclines (25%) (6).

In a Canadian trial reported by Levine et al. (15) premenopausal, node-positive patients were randomized between adjuvant treatment with intensive FEC (fluorouracil, epirubicin, cyclophosphamide) versus CMF. At a median follow-up of 37 months, relapse-free survival was improved by 9% among patients receiving intensive FEC compared to those who received CMF (71% vs. 62%) whereas the 3-year survival was similar in the two groups (84% vs. 83%). It is unclear whether the observed benefit was due to the use of an anthracycline or the increased overall drug delivery.

A well-documented problem with anthracyclines is their carcinogenic potential. In the Canadian trial there were 4 cases of acute leukemia, all in the epirubicin group: 3 cases were classified as acute myeloid leukemia, and one as an acute lymphoblastic leukemia.

CHEMOTHERAPY-ASSOCIATED LEUKEMIA

There are some drugs frequently used in breast cancer chemotherapy that have an established leukomogenic potential: alkylating agents such as melphalan and cyclophosphamide, and topoisomerase II-inhibitors such as anthracyclines. Leukemia associated with alkylating agents typically have a relatively long latency from initiation of treatment, a preleukemic phase (e.g. myelodysplastic syndrome (MDS)) and is frequently associated with cytogenetic abnormalities on chromosomes 5 and 7. In contrast, topoisomerase II-associated leukemia typically has a short latency, no preleukemic phase, and abnormalities on chromosome 11.

At the NIH consensus development conference on adjuvant chemotherapy for breast cancer in 1985 it was concluded that adjuvant treatment with melphalan for 2 years was associated with a risk of acute myelogenous leukemia (AML) or MDS of 1.7% compared with 0.3% among women not receiving such treatment (16). It was also concluded that the use of other alkylating agents such as cyclophosphamide had not at the time been reported to be associated with an increased risk. This conclusion was supported in a 1995 paper from the Eastern Cooperative Oncology Group (ECOG) (17). They reported their experience with standard dose-intensity CMF-type regimens in six controlled clinical trials during 1978–1987. At a median follow-up of 7 years they observed 3 cases of MDS, and 2 cases of AML among 2600 patients for an estimated incidence of MDS + AML of 0.03%. They concluded that the risk of secondary myeloproliferative disease among patients receiving standard dose cyclophosphamide-containing regimens was not much higher than expected for an age-matched general population. The University of Texas-M D Anderson Cancer Center experience with standard dose-intensity FAC treatment was reported in 1996 (18). In contrast to the ECOG results, they observed a total of 14 cases of leukemia among 1474 patients at a median follow-up of 8 years for an estimated incidence of 1.5%. The leukemia risk appeared to be higher if the treatment was given in combination with radiation therapy (2.5% vs. 0.5%, $p = 0.01$) or with cumulative cyclophosphamide doses in excess of 6 g/m^2 (2.0% vs. 1.3%, $p = 0.5$). At the annual meeting of the American Society of Clinical Oncology in 1997 the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported the incidence of AML and MDS among patients included in their B-22 study (19), which is a controlled trial that assesses the clinical relevance of cyclophosphamide dose intensity and cumulative dose in the context of adjuvant AC (doxorubicin, cyclophosphamide) therapy. They found a 4-year cumulative incidence of myeloproliferative disease of 0.9% which was greater than in previous NSABP studies using standard dose cyclophosphamide. The cytogenetic examinations indicated a mixture of early cases (probably related to adriamycin), and later cases probably related to cyclophosphamide.

In conclusion, standard dose adjuvant CMF-type regimens are associated with a low risk of leukemia or MDS which is probably not much different from the risk in a general population. In contrast, melphalan, standard dose

anthracyclines, and increased dose-intensity or high cumulative dose cyclophosphamide seem to be associated with some increase in the risk. With standard dose anthracyclines the cumulative risk 4–8 years after primary treatment seems to be in the order of 1–2%. At present there are no statistically reliable data available on the risk of leukemia associated with the use of dose-escalated anthracyclines but the risk appears to be greater than with standard doses.

The risk of secondary leukemias associated with the use of some types of adjuvant chemotherapy should obviously be viewed in relation to the treatment benefit that can be achieved. The best estimate of the benefit associated with the use of anthracycline-containing regimens is probably that generated by the overview of chemotherapy trials. As mentioned, the mortality odds reductions achieved with standard dose CMF-type seem to be roughly the same as that achieved with anthracycline-containing regimens. These observations together with the well-established cardiotoxicity of anthracyclines cast some doubt on their role in the adjuvant setting.

DOSE ESCALATION

Perhaps the most controversial issue today in the field of chemotherapy of both recurrent and primary breast cancer is the relevance of drug dose and dose intensity. Very intense regimens require hospitalization, autologous bone marrow transplantation or peripheral stem-cell support, and are extremely expensive compared to conventional regimens. Moreover, high-dose treatment is associated with a mortality that is not insignificant although very low in the hands of experienced oncologists. Problems with dose-intense anthracycline regimens include, as mentioned, treatment-related leukemia.

A recent trend in medical oncology is to administer higher than standard chemotherapy doses in order to improve treatment results. The basic assumption is that with conventional doses of most cytotoxic agents we are still on the steep upward part of a sigmoid dose-response curve. However, in humans there is only little information available on whether this assumption holds true. In the late 1980s Hryniuk et al. published retrospective analyses of chemotherapy trials in advanced disease (20). There appeared to be a positive correlation between the dose intensity of the regimens used in the trials and the outcome in terms of objective response rate. Dose intensity was defined as the average amount of drug/m^2/unit of time. These results contributed to an increased interest in dose escalation. However, to date only a few prospective, controlled trials have been published.

There are two studies of standard versus lower than standard dose intensity CMF in metastatic breast cancer including c. 400 patients (Table 2) (21, 22). Both trials showed a superior median survival for patients allocated to standard dose intensity. A similar finding with lower than standard dose intensity FAC chemotherapy was reported by Wood et al. in the adjuvant setting (23). Higher than standard versus standard dose intensity FAC or AC treatment was compared in 3 trials (23–25). None of these trials showed convincing evidence of improved survival with the intense regimen.

Dose-intense chemotherapy requiring stem-cell transplantation in patients with metastatic breast cancer has been studied in two trials comprising a total of 188 patients (Table 2). The first trial, reported in 1995 by Bezwoda et al. (26), showed a significant increase in median survival from 45 to 90 weeks with the high-dose regimen. In the preliminary report by Peters et al. (27) patients allocated to immediate high-dose therapy after a complete response to induction chemotherapy had a significantly longer disease-free survival than the control patients who received high-dose treatment first at relapse. However, the overall survival was better for the controls. Trials of dose-intense chemotherapy requiring hematological rescue in the adjuvant setting are underway but no results are yet available.

The published studies on dose escalation were recently summarized and reviewed by Savarese et al. (28, 29). Their conclusion was that lower than standard doses of CMF, FAC, or AC seems to be associated with a poorer outcome but that higher than standard doses have not been convincingly shown to improve overall outcome.

DRUG SEQUENCING

An innovative strategy to circumvent drug resistance is alternating therapy. The Milan group compared 4 courses of doxorubicin followed by 8 courses of CMF (sequential regimen) with 2 courses of CMF alternated with one course of doxorubicin for a total of 12 courses (alternating regimen) (30). The trial included c. 400 patients with > 3 positive lymph nodes. Patients allocated to the sequential regimen had a significantly improved relapse-free and overall survival than patients in the alternating regimen (42% vs. 28%, $p = 0.002$, and 58% vs. 44%, $p = 0.002$, respectively). These results remain tentative until supported by other studies.

Preliminary data suggest that alternating endocrine regimens may also be beneficial. In a Norwegian study of metastatic disease, alternating treatment with tamoxifen and megestrol acetate in 2-month cycles resulted in a higher objective response rate than tamoxifen alone (31). Whether this observation holds true in the adjuvant setting is currently being tested in the context of controlled trials in Scandinavia (32).

TIMING OF TREATMENT

Theoretically, it should be more advantageous to initiate chemotherapy as soon as possible, that is, immediately

after primary diagnosis and before definitive surgery. This is often referred to as 'neoadjuvant' chemotherapy. The possibility of eradicating micrometastases should theoretically be the best when the tumor burden is the smallest. A reduction in the size of the primary tumor might also permit or facilitate breast-conserving surgery. In laboratory animals surgical removal of a tumor may cause dissemination of malignant cells into the bloodstream. This observation was the main rationale for several trials of perioperative therapy.

In a Scandinavian study during the 1960s, perioperative cyclophosphamide reduced the incidence of distant metastases and significantly improved the overall survival (33). However, recent updates of the Scandinavian trial, and trials by the Cancer Research Campaign (CRC) (34), the International Breast Cancer Study Group (IBCSG) (35), and several other groups (36), have demonstrated conclusively that, although there may be some benefit with perioperative therapy, its effect is only minor and significantly inferior to that of more prolonged postoperative cytotoxic treatment. Moreover, in the IBCSG trial there was no difference between the patients who received postoperative CMF therapy and those who also received perioperative CMF. These observations suggest that very early initiation of treatment is probably of minor importance. This conclusion was confirmed by the recently published NSABP B-18 trial which included patients with stage I–II breast cancer (37). The trial compared the same chemotherapy given either before or after surgery. Although there was a high local response with the chemotherapy, there was no statistically significant benefit in terms of either disease-free or overall survival with neoadjuvant treatment. On the other hand, the NSABP trial together with several other studies have clearly demonstrated that the high local response to neoadjuvant chemotherapy results in an increased proportion of patients who might be candidates for breast-conserving surgery.

Neoadjuvant chemotherapy permits monitoring of the response to treatment either as local objective response or through repeated analyses of, for instance, the proportion of proliferating cells in the tumor before and after initiation of therapy. A preliminary report by Skoog et al. showed that patients treated with neoadjuvant chemotherapy who experienced a decrease in the proliferating fraction after the first course of treatment had a significantly better recurrence-free survival than patients in whom a decrease was not observed (38). This suggests that the response to neoadjuvant chemotherapy possibly could be used to identify patients who will benefit the most from more chemotherapy. However, this conclusion remains speculative until supported by further data.

TAXANES

The taxanes represent a novel class of cytotoxic substances. Taxol and taxotere are currently the only commercially available drugs of this type. Both taxanes have a broad anti-neoplastic activity and are highly active as single agents in patients with metastatic breast cancer. Taxol and taxotere have overlapping, although not identical, pharmacological profiles (39). There is no trial that has directly compared the activity of the two drugs. However, indirect comparisons of trials seem to indicate a somewhat higher activity of taxotere in terms of objective response in patients with metastatic disease. A problem particular to taxol seems to be cardiotoxicity, which has not been reported with taxotere. The benefits of taxanes may be more evident if applied in the adjuvant setting when the tumor burden is less. With recent improvements in our ability to handle the most troublesome acute side effects of the two taxanes (allergic reactions with taxol versus fluid retention with taxotere), and the rapid development of multi-drug, taxane-containing regimens, adjuvant taxane therapy may well prove to be a significant progressive step. Although controlled trials of adjuvant taxane treatment are underway, no results are yet available.

CASTRATION

The first randomized trial of prophylactic ovarian ablation was started in 1948 at the Christie Hospital in Manchester (40). This study was followed by several similar trials. Early results were contradictory but seemed to indicate that treated patients in general had a longer disease-free interval but that overall survival was not significantly prolonged. This was interpreted to suggest that the treatment could be deferred until recurrence thereby avoiding over-treatment in non-responding patients or patients not at risk of recurrence. However, a recent overview of the ovarian ablation trials, comprising a total of about 2100 patients aged under 50 years, indicated a significant overall survival benefit (41). At 15 years the overall survival benefit among patients who did not receive chemotherapy was 6% among node-negative patients and 13% among node-positive patients, which corresponds to a relative reduction in mortality of about 24%. Thus, both in relative and absolute terms the benefit was roughly similar to that achieved with adjuvant chemotherapy. In the presence of chemotherapy, the benefit of adding ovarian ablation was less (relative reduction in mortality of 8%) and not statistically significant.

The real effect of ovarian ablation appears to have been obscured in the individual studies by too small sample sizes. Given the results of the overview, ovarian ablation deserves re-examination as adjuvant therapy for premenopausal women, particularly since at least part of the effect of adjuvant chemotherapy may be mediated through

endocrine mechanisms. However, castration is associated with several adverse side effects such as hot flushes, vaginal dryness, bone demineralization, and possibly an increased risk of cardiovascular disease. In recent years it has become possible to induce a reversible castration by the use of LHRH analogues. Trials are currently underway that aim to determine the role of a few years' adjuvant treatment with LHRH analogues in premenopausal patients and whether there is a benefit with castration in the presence of long-term tamoxifen (42).

TAMOXIFEN

The low acute toxicity of tamoxifen has made it the most common endocrinologically active drug used in the adjuvant setting. The number of patients included in randomized adjuvant tamoxifen trials initiated before 1985 is about 32000 The number of patients included in trials testing other types of additive endocrine therapy is comparatively minor, only about 3000 (6).

The majority of patients included in tamoxifen trials have been postmenopausal and aged above 50 years. In the overview published in 1992 there appeared to be a interaction between the effect of tamoxifen and patient age: the overall survival benefit with tamoxifen in women over 50 years was highly significant, whereas the estimated benefit was smaller and not significant among those under 50 years. It may be hypothesized that this could be due to the higher levels of circulating estrogens in premenopausal women, or an interaction between tamoxifen and chemotherapy. In several trials including large numbers of young women, tamoxifen was administered concurrently with adjuvant chemotherapy. There are preclinical data to suggest that tamoxifen may decrease the sensitivity of breast cancer cells to cytotoxic therapy by inducing cell cycle arrest (43). Another puzzling observation in the overview was the purely quantitative interaction between tamoxifen therapy and estrogen receptor status: the tamoxifen effect was less pronounced, but still present, also in women with tumors classified as estrogen receptor negative. However, in the 1995 update of the overview the benefit with tamoxifen in women aged under 50 years was almost as great as the benefit among the older women (8). The earlier results may simply have resulted from confounding from length of treatment: many trials including premenopausal women used shorter durations of tamoxifen than trials including large numbers of postmenopausal patients.

In the 1995 update the interaction between tamoxifen and estrogen receptor status had become more pronounced, at least among women aged under 50 years. Among estrogen receptor-negative women aged under 50 years the relative reduction in events with tamoxifen was only x% and the reduction in mortality x%. These results support the hypothesis that the lack of correlation between estrogen receptor status and benefit with tamoxifen in the early reports from the overview may have been related to misclassification of ER status due to technical difficulties with the assays during the 1970s and early 1980s in many centers.

The 'first generation' adjuvant tamoxifen trials compared treatment with tamoxifen for 6 months up to 5 years with no adjuvant endocrine therapy. This implied that none of these studies could define the optimal duration of treatment. Recently, several trials have been published that have directly compared different treatment durations (44–47). The Swedish trial included c. 3500 patients randomized between 2 and 5 years of tamoxifen (44). At a median follow-up of $5\frac{1}{2}$ years there was a statistically significant overall survival benefit for patients allocated to 5 years of treatment, which corresponded to a relative reduction of deaths of about one-fifth. In two other randomized trials comprising a total of c. 1200 patients, the value of prolonging adjuvant tamoxifen beyond 5 years was tested (46, 47). None of these studies have demonstrated any significant benefits for those patients who were allocated to the longer duration. In fact, in one of the studies recurrence-free and overall survival was actually slightly inferior among patients allocated to 10 years of treatment compared with those who stopped therapy at 5 years (46). This observation may represent a clinical correlate to preclinical observations of tumor growth stimulation with tamoxifen. However, the number of patients required in order reliably to either confirm or refute a clinically worthwhile benefit with tamoxifen prolonged beyond 5 years is probably in the order of 15000 to 20000. Since the current number is only c. 1200, the optimal duration of tamoxifen remains an open question, although 5 years appears to be the standard today in most centers.

It has quite recently been appreciated that tamoxifen, in addition to its antitumor effects, also has both potentially beneficial and adverse long-term side effects. Low-density lipoprotein cholesterol and lipoprotein (a) are significantly diminished with standard daily doses of tamoxifen in postmenopausal women (48). In one randomized trial tamoxifen was associated with a significantly decreased incidence of acute myocardial infarctions (49). In another trial tamoxifen significantly reduced cardiac morbidity in terms of hospital admissions due to ischemic heart disease (50). In postmenopausal patients tamoxifen diminishes lumbar spine demineralization (51) which may translate into a decreased incidence of fractures in women on long-term tamoxifen. On the other hand, from other studies there have been reports of tamoxifen-associated increases in thrombembolic events (e.g. (52)). In addition, several trials have confirmed an increased incidence of endometrial cancer associated with tamoxifen (8). There is still considerable uncertainty about the absolute size of this adverse effect: in current reports the relative risk estimate varies between 2 and 6. There is also continued uncertainty

concerning the biologic behavior of tamoxifen-induced endometrial cancers. One study claimed that they in general were more often high-grade with a poorer prognosis (53), whereas other studies have suggested that they are similar to other types of endometrial cancer. A joint analysis of three Scandinavian adjuvant tamoxifen trials showed a significant increase in endometrial cancer but also an increase in gastrointestinal cancer, particularly colorectal cancer, among the tamoxifen-allocated patients (54). No trial has to date verified an increase in primary liver cancer despite the fact that tamoxifen causes DNA adduct formation in rodent liver. In the latest update of the overview, non-breast cancer mortality was similar among tamoxifen-allocated and control patients (except for mortality due to endometrial cancer) (8).

The carcinogenic properties of tamoxifen cast some doubt on the utility of the drug as a chemopreventive agent in healthy women. Alternative endocrine agents without genotoxic potential are theoretically more attractive. However, randomized chemopreventive tamoxifen trials are currently underway in both the US and Europe.

In summary, in the adjuvant setting it is clear that the benefits of a few years of adjuvant tamoxifen seem to outweigh the reported risks. However, whether this also holds true in the chemopreventive setting remains an open question. Considering the pharmacological profile of tamoxifen with its partial agonistic estrogenic properties, potential for tumor growth stimulation, DNA-adduct forming ability (55), risk of thrombembolic disease and carcinogenesis, there is clearly a need for trials testing the benefits of more modern endocrinological agents such as the new generation of non-steroidal antiestrogens, pure antiestrogens, and the new generation of aromatase inhibitors. The relevance of concurrent, sequential, or alternating multi-drug endocrine therapy also remains an open question.

PROGNOSTIC AND PREDICTIVE FACTORS

In clinical decision-making, identification of high- and low-risk subsets of patients is an important issue. The absolute risk of recurrence and death must be viewed in relation to the potential benefit with a particular adjuvant therapy. A vast number of new putative prognostic factors have been investigated during the past 10–15 years. Some are suggested to be of relevance in making treatment decisions. Current discussions about the selection of patients for adjuvant systemic therapy have mainly focused on node-negative patients. Unfortunately, no single prognostic parameter seems able to identify a subgroup of node-negative patients without risk of disease recurrence. There is also no universal consensus on which factors are optimal in identifying a high-risk subset (56). In recent years there has been increasing recognition of the fact that treatment-predictive factors may be of more clinical relevance. Today there is only solid clinical documentation for one set of treatment-predictive factors, viz. hormone receptors for the selection of patients likely to benefit from endocrine therapy (57). However, other factors have also been proposed; for instance, S-phase fraction (58) and c-erbB-2-over-expression (59) to predict the effect of chemotherapy and endocrine therapy, and markers of apoptosis (bcl, bax, etc.) to predict endocrine responsiveness (60). However, the clinical relevance of these new molecular markers remains obscure and can only be adequately assessed in the context of prospective, controlled clinical trials.

CONCLUSIONS

In the past 10–15 years there has been significant progress in the field of systemic adjuvant therapy of breast cancer. It is now reliably established that the concept is valid; that is, that early treatment does result in improved survival compared to treatment deferred until relapse. This fact has been established for cytotoxic chemotherapy as well as endocrine therapy. However, several issues regarding the optimal way to administer currently available drugs as well as the clinical relevance of several new drugs remain controversial. The benefit in absolute terms with the treatments that are available today remains modest although clinically worthwhile in many patient subsets. Major breakthroughs in the identification of new prognostic and/or predictive tests are still to come.

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