Dose-Dense and Sequential Strategies in Adjuvant Breast Cancer Therapy

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Several attempts have been made to improve the survival rates of breast cancer patients. The benefit of adjuvant chemotherapy was clearly shown, but the absolute difference of 2% to 11% in overall survival, depending on the

Introduction

Data from the meta-analysis of the Early Breast Cancer Trialists’ Collaborative Group regarding adjuvant chemotherapy clearly showed the benefit of adjuvant chemotherapy.[1] The absolute difference in overall survival (OS) of 2% to 11%, depending on the patient group, is, however, disappointingly small. In particular, high-risk patients, for example patients with ≥ 10 involved lymph nodes, extracapsular spread, or vascular invasion, still have an excessive risk of recurrence even after standard adjuvant chemotherapy. To increase the survival rates after adjuvant therapy, new chemotherapeutic agents and new strategies of application are being evaluated in clinical trials.

From CMF to Anthracyclines

Chemotherapy with cyclophosphamide (Cytoxan, Neosar), methotrexate, and fluorouracil (CMF), as shown by Bonadonna et al, produces the greatest benefit in patients with one to three involved lymph nodes, but is of limited efficacy in patients with four or more involved lymph nodes.[2] Overall survival rates with CMF in this study were 38% after 20 years for patients with one to three positive lymph nodes and 24% for untreated patients with one to three positive lymph nodes. CMF-treated patients with more than three positive lymph nodes had virtually the same survival rate as controls (24% vs 23%).

Even anthracycline-containing regimens in standard dose are of limited efficacy in high-risk patients with 10 or more involved lymph nodes.[3] In an Italian study, for example, 10-year follow-up data showed that sequential treatment with four cycles of doxorubicin 75 mg/m² every 3 weeks followed by eight cycles of CMF was superior to alternating treatment with doxorubicin and CMF at the same total drug doses. However, overall survival in patients with 10 or more lymph nodes was the same regardless of whether patients had received sequential or alternating treatment.

Because even CMF is associated with a significant rate of severe adverse events, it is highly questionable whether one should advise patients to undergo such treatments when no major success can be expected. The duration of treatment is approximately 6 months, and the increase in survival time or disease-free survival (DFS) should be substantially longer to justify the increased side effects.

New Strategies Suggested

To address these shortcomings, several strategies have been suggested and partially evaluated in clinical trials. The use of high-dose chemotherapy with bone marrow transplantation (BMT) or peripheral blood progenitor cell (PBPC) support remains controversial due to the small number of prospective, randomized trials comparing it with standard therapy. Gianni et al,[4] who assessed high-dose chemotherapy in patients with 10 to 20 positive lymph nodes, found a 20% improvement in DFS after 5 years when compared with a historical patient group treated with CMF.

Although some promising results were presented at the American Society of Clinical Oncology
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(ASCO) meeting in 1999, an external audit of this trial could not verify these results.[5, 5a]. High-dose therapy with PBPC support for high-risk breast cancer cannot be recommended at present. The rate of serious adverse events, including fatalities, is still enormous. Depending on the toxicity of the regimen, treatment-related death rates can be as high as 5%.[6] The risks of secondary malignancies and treatment-related concurrent diseases, as well as the effects of such treatments on the immune system, remain uncertain.

A similar, but less radical, strategy is the intensification of standard chemotherapy. This can be achieved by several means.[7] The limiting factor for all attempts at dose intensification is toxicity, mainly hematotoxicity. Higher doses lead to lower granulocyte nadirs and a higher incidence of febrile neutropenia. Shortening of cycle intervals is limited by the recovery of blood counts. The introduction of hematopoietic growth factors, such as recombinant granulocyte colony stimulating factor (r-metHuG-CSF) and erythropoietin, has helped to overcome some of the limitations. Dhingra et al and others showed that by using r-metHuG-CSF, the intended dose could be achieved more easily.[8]

### Dose Intensification

Several chemotherapeutic agents have shown a relevant in vitro dose-response relationship. In patients with metastatic disease, dose-intensified chemotherapy could achieve higher remission rates.[9,10] According to a retrospective analysis of 901 patients done by Bonadonna and Valagussa, only those who received at least 85% of the planned CMF dose benefited from adjuvant chemotherapy. Patients who received less than 65% of the planned dose had DFS and OS similar to that in the untreated control group.[11]

Several prospective, randomized studies of dose-intensified chemotherapy have been published. Three trials evaluated dose-intensified anthracyclines (doxorubicin, epirubicin [Ellence]).[12-14] The French Adjuvant Study Group compared the combination of fluorouracil (5-FU), epirubicin, cyclophosphamide (FEC) (500/50/500 mg/m² q3wk) with an epirubicin-intensified FEC (500/100/500 mg/m² q3wk) regimen in high-risk breast cancer patients. The findings of this study suggested that dose escalation of epirubicin without use of granulocyte colony stimulating factor (G-CSF) generates a significant improvement in OS and DFS.[12]

The National Cancer Institute of Canada Clinical Trials Group was the first to show a significant improvement in DFS and OS in premenopausal patients with involved axillary lymph nodes. This study compared dose-intensified CEF (75 mg/m² po days 1-14, 60/500 mg/m² days 1+8, q4wk × 6) with a standard CMF (100 mg/m² po days 1-14, 40/600 mg/m² days 1+8, q4wk × 6) therapy.[13] Keeping in mind that National Surgical Adjuvant Breast and Bowel Project (NSABP)-15 showed that equitoxic doses of Adriamycin (doxorubicin)/cyclophosphamide (AC) and CMF were equally effective as adjuvant therapy for node-positive breast cancer patients, the superior efficacy seen in this trial could likely be based on the use of dose-intensified epirubicin.[14] Alternative hypotheses involve the presence of fluorouracil in the FEC regimen, compared to AC/EC, and the administration of six cycles for FEC, compared to four cycles for AC/EC.

Another clinical trial that has demonstrated a significant benefit in OS and DFS for a dose-intensified anthracycline-containing regimen was the Cancer and Leukemia Group B (CALGB) 8541 protocol. In this study, DFS was 75% after 3 years in patients receiving FEC (600/60/600 mg/m² q4wk × 4) while it was 65% in patients receiving FEC (400/40/400 mg/m² q4wk × 4). Dose-related differences in outcome were observed exclusively in the HER2-positive population. The total dose was identical in both treatment groups while the dose intensity was higher in the first group. In a third group, patients received half the total dose of the two other groups at half the dose intensity of the first group, and they had the worst outcome.[15]

### Sequential Therapy

Another promising treatment strategy for breast cancer is the sequential application of chemotherapeutic agents. In 1995, Bonadonna published results of a trial demonstrating the superior effects of sequential vs alternating application at the same total drug doses. In this study,
sequential administration of doxorubicin followed by CMF proved significantly beneficial compared with alternating doxorubicin/CMF therapy. In the sequential arm, 10-year DFS was 42% and 10-year OS was 58%, while in the alternating arm, the respective rates for DFS and OS were 28% and 44%.[3]

In addition to its positive effects on survival, sequential therapy seems to have an advantage in terms of overlapping toxicities often experienced by patients receiving combination chemotherapy regimens. Thus, sequential administration allows for dose escalation of non-cross-resistant agents to an optimal dose.

To evaluate dose-intensified doxorubicin (Adriamycin) (A) with sequential paclitaxel (Taxol) (T) as adjuvant therapy, CALGB trial 9344 was initiated in 1994. This large study compared three different dose intensities of an AC regimen, containing 60, 75, or 90 mg/m^2 doxorubicin, given every 3 weeks. To evaluate the additional benefit of paclitaxel, patients were randomized a second time (Figure 1). The outcome of this study showed no difference in the AC regimens based on doxorubicin dose intensity, whereas the addition of sequential paclitaxel significantly reduced the relative risk of disease recurrence (22%) and death (26%).[16]

Epirubicin Permits Dose Escalation of Anthracyclines

The availability of epirubicin, an agent equally effective as doxorubicin, but less cardiotoxic, has permitted dose escalation of anthracyclines in adjuvant therapy without serious cardiotoxic effects.

Trial of Dose-Intensified vs Sequential Regimens

We conducted a randomized trial to evaluate the feasibility and efficacy of a dose-intensified epirubicin and cyclophosphamide regimen, as compared with a standard-dose regimen of sequential epirubicin/cyclophosphamide (EC) and CMF (Figure 2). Patients from four centers in Germany who had 10 or more involved lymph nodes or extracapsular spread to the lymph nodes[17] were entered in the trial. The control arm (EC/CMF) was a modification of the sequential doxorubicin/CMF regimen of Bonadonna et al,[3] and consisted of four cycles of EC (90/600 mg/m^2 q3wk) followed by three cycles of intravenous CMF every 4 weeks (500/40/600 mg/m^2 days 1+8). Radiation of locoregional lymph nodes and, in cases of breast-conserving therapy, radiation of the breast, was performed between the EC and the CMF cycles.

The dose-intensified experimental arm ( DI-EC) consisted of four cycles of EC (120/600 mg/m^2 q2wk). To avoid delays in the administration of the next cycle due to hematotoxicity, r-metHuG-CSF (filgrastim 5 mg/kg/d) was given prophylactically on days 2-12 of each cycle. Filgrastim could be discontinued when the white blood cell count nadir was passed and the count was more than 15,000. Radiation therapy was performed after chemotherapy. Postmenopausal patients with positive hormone receptors were offered tamoxifen 30 mg daily for 5 years, and premenopausal women could receive gonadotropin-releasing hormone (GnRH) analogs for 2 years.

At the time the study was closed (September 1997), 183 patients had been recruited. A first interim analysis was performed then with a median follow-up of 23 months, and results were presented at the first European Breast Cancer Conference in Florence, Italy, in 1998.[17] Among 183 enrolled patients, 174 were evaluable for survival. Of these, 91 had received DI-EC and 83, EC/CMF. Thirty-eight patients had disease recurrence and 18 died; 25 recurrences were in the EC/CMF arm and only 13 in the DI-EC arm. Mean DFS was 37.7 months for EC/CMF and 46.4 months for DI-EC, a significant difference ($P = .04$). Seven patients in the DI-EC arm vs 11 among the controls died; this difference was not statistically significant at the time of interim analysis. The final results of this trial are being evaluated and have been submitted for publication. A re-analysis with overall survival as a major target is under evaluation.

Toxicities in the Two Arms

Hematologic toxicity, monitored by twice-weekly blood counts, occurred more frequently with DI-EC. Despite r-metHuG-CSF-support, grade 4 leukopenia occurred in 8.3% of all evaluable DI-EC cycles.
and grade 3 leukopenia in 13%. With EC/CMF, grade 3 leukopenia was relatively frequent (nearly 22%) but grade 4 was virtually absent (one episode). Febrile neutropenia rarely occurred (three episodes) in the EC/CMF arm. Thrombocytopenia was of minor importance: in 353 evaluable cycles, 11 episodes of grade 2 to 4 thrombocytopenia was observed with DI-EC, and none with EC/CMF.

In contrast, treatment-induced anemia was substantial in the dose-intensive arm. The median decrease of hemoglobin level during chemotherapy was 2.8 g/dL in the DI-EC arm compared with 1.1 g/dL in the control arm. The treatment resulted in grade 2 to 4 anemia in 16% of the patients treated with DI-EC.

The most common nonhematologic toxicities were nausea and vomiting. Among DI-EC-treated patients, 41% reported slight, 10% reported moderate, and 2% reported severe nausea, while only 26% of all EC/CMF patients had slight and 5% had moderate nausea. Vomiting occurred 3.5 times more frequently with DI-EC. Routine antiemetic prophylaxis with potent 5-HT3 antagonists and corticosteroids was administered.

Quality of life (QOL) was analyzed with the European Organization for the Research and Treatment of Cancer and linear analog self-assessment tools (EORTC-LASA). Although most QOL indices were similar for the two treatments, ability to work ($P = .05$) and mood ($P = .03$) were significantly better, and activity was marginally better with DI-EC ($P = .07$) than with EC/CMF treatment.

**Other Related Trials**

Figure 3 depicts the design of our trial of neoadjuvant therapy in which 500 of the planned 570 patients have been recruited so far. Using strategies of dose-intensified and dose-dense drug administration, we compared four cycles of neoadjuvant ET (epirubicin/paclitaxel [Taxol]; 90/175 mg/m² q3wk) with three cycles of sequential, neoadjuvant epirubicin (150 mg/m² q2wk) followed by three cycles of paclitaxel (250 mg/m² q2wk). Patients in both treatment arms received three cycles of CMF (500/40/600 mg/m² q4wk) after surgery. Hematologic and nonhematologic toxicity data are shown in Table 1 and Table 2 (Untch M et al: ASCO 2001, accepted for publication). Further results of this study will be available in 2001.

Following evaluation of response rates in this neoadjuvant trial, our study group will begin a new trial for patients whose tumors overexpress HER2/neu. Patients receiving a treatment arm consisting of EC followed by paclitaxel[16] will be randomized for concomitant, neoadjuvant trastuzumab (Herceptin).

The German Gynecologic Oncology Group is currently conducting a trial evaluating the cardiac safety of trastuzumab in combination with epirubicin/cyclophosphamide as first-line therapy for patients with HER2/neu overexpressing metastatic breast cancer. The frequency and severity of cardiac toxicities observed in this trial will help determine whether this combination can be used in the neoadjuvant and adjuvant settings.

Another multicenter trial based on the concept of sequential, dose-intensified, adjuvant therapy is also being conducted in Germany (Figure 4). Patients with four or more involved lymph nodes are randomized to receive four cycles of EC (90/600 mg/m² q3wk) followed by four cycles of paclitaxel (175 mg/m²), or a sequential regimen of three cycles of epirubicin (150 mg/m² q2wk) followed by three cycles of paclitaxel (225 mg/m² q2wk) followed by three cycles of cyclophosphamide (2,500 mg/m² q2wk). Patients in the sequential treatment arm all receive G-CSF and are randomized a second time for treatment with erythropoietin or not. So far, almost 650 of a planned 800 patients have been accrued.

A previous phase I/II study including 102 patients conducted by the same study group showed tolerable side effects for sequential, dose-intensified ETC (epirubicin at 120-150 mg/m², paclitaxel at 200-250 mg/m², cyclophosphamide at 2,000-3,000 mg/m²) supported by G-CSF. Patients were treated at seven different dose levels.

Dose-limiting grade 3 neurotoxicity was seen in 10 of 49 patients at a paclitaxel dose of 250 mg/m². Hematologic toxicity was mild and varied among agents and dose levels. No clinically significant or
measurable cardiac toxicity was observed. A total of 28% of patients received transfusions, two
patients required platelet support, and only nine cases of febrile neutropenia occurred. At a median
follow-up of 18 months, seven patients have had disease relapse.[18]

Conclusions and Implications

The efficacy of standard CMF chemotherapy as the adjuvant treatment of breast cancer was
demonstrated by Bonadonna et al. Nevertheless, high-risk patients still have an excessive risk of
recurrence even after standard adjuvant chemotherapy. To increase DFS and OS in these patients,
new therapeutic approaches are needed. Dose-intensification and dose-dense application of
chemotherapy are among the concepts being investigated.

In our trial, patients receiving dose-intense EC chemotherapy with r-metHuG-CSF-support had a
significant advantage in DFS compared with those receiving standard-dose EC/CMF, with a median
follow-up of 2 years. So far there has not been a significant improvement in OS; longer follow-up is
needed to determine the impact on survival, and this is under investigation.

We have been unable to determine whether the observed differences in results are due to increased
dose intensity or total dose. There are attractive theoretical principles supporting the concept of
increased dose intensity,[16] but total dose may also be an important determinant, at least for
anthracyclines. This latter hypothesis is supported by findings from a CALGB study of different doses
and dose intensities of CAF (cyclophosphamide, Adriamycin, and fluorouracil) chemotherapy.[15]

In our study, the toxicity of DI-EC was acceptable, less than would be expected with high-dose
chemotherapy with peripheral blood stem cell support. The tolerability of DI-EC was generally good.
Furthermore, the short duration of DI-EC treatment (approximately 8 weeks) compared with that of
other effective regimens (approximately 20 weeks) is attractive for most patients.

In a study by the French Adjuvant Study Group, significantly higher DFS and OS were seen in
patients who received dose-escalated epirubicin (100 mg/m$^2$) without G-CSF support compared to
lower-dose epirubicin (60 mg/m$^2$). The results of the National Cancer Institute of Canada Clinical
Trials Group showed the superiority of dose-intensified CEF over CMF in terms of both DFS and OS.
The findings of this large study led to the approval of epirubicin in Canada and the United States.

Current and future studies will help to define the use of sequential dose-intense regimens with
epirubicin, paclitaxel, and cyclophosphamide with r-metHuG-CSF and erythropoietin support
compared with "standard" therapies in the adjuvant and neoadjuvant settings. A nonrandomized
clinical trial in high-risk breast cancer patients, being conducted at our institution, is evaluating the
potential role of erythropoietin in reducing chemotherapy-induced anemias in patients receiving
dose-intensified EC (120/600 mg/m$^2$ q2wk × 4) plus G-CSF (Figure 5).

Assessing New Strategies

Worldwide, several trials are assessing new strategies in the treatment of breast cancer. One of the
most promising concepts, which has already demonstrated efficacy in various trials, is sequential
administration of dose-dense chemotherapy, as used in the adjuvant and neoadjuvant trials of the
German Gynecologic Oncology Group (Figure 3 and Figure 4). The initial results of these studies
showed that dose-intensified sequential therapy using epirubicin and paclitaxel is feasible for
high-risk breast cancer patients, and is associated with tolerable side effects.

The National Cancer Institute of Canada Clinical Trials Group is comparing three different therapies
in the MA.21 trial. The first treatment arm consists of six cycles of FEC (F 500 mg/m$^2$ days 1+8, E 60
mg/m$^2$ days 1+4, C 75 mg/m$^2$ days 1-14 q4wk). The second arm consists of four cycles of AC (60/600
mg/m$^2$ q2wk) followed by four cycles of paclitaxel (175 mg/m$^2$ q3wk). The third arm consists of six
cycles of EC (E 120 mg/m$^2$ days 1+15, C 830 mg/m$^2$ days 1+8 q3wk) followed by four cycles of
paclitaxel (175 mg/m$^2$ q3wk). In this third arm, patients are also treated with erythropoietin and
receive G-CSF support during epirubicin cycles.
These studies may help to identify the most effective and feasible combinations and strategies in adjuvant treatment of breast cancer. New trials combining trastuzumab, epirubicin, and paclitaxel will be conducted in the near future if data from an ongoing trial using trastuzumab and epirubicin in metastatic breast cancer patients prove the feasibility of this therapy. Only if new concepts, supportive agents, and chemotherapies find their way into randomized clinical trials will we be able to determine the best possible treatments for our patients.

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