Dose Intensity for Breast Cancer

Review Article [1] | June 01, 2001
By Deborah K. Armstrong, MD [2] and Nancy E. Davidson, MD [3]

Despite nearly 20 years of study, the importance of chemotherapy dose intensity in breast cancer remains unclear. Substantial preclinical data suggest a dose-response relationship, and consistent data document that

Introduction

Improvements in cancer screening and therapy have led to earlier detection and a reduction in the mortality of breast cancer over the past 2 decades. Despite this progress, one in eight American women who live to age 85 will develop breast cancer. Furthermore, breast cancer remains a leading cause of death in women between the ages of 15 and 54.[1-3] In an attempt to improve the outcome of therapy for breast cancer, researchers and clinicians have examined the use of higher doses of effective anticancer agents. Substantial in vitro and animal data support the concept that increasing drug dose is an effective method of increasing tumor cell kill.[4] These models, however, frequently indicate a plateau, above which increases in drug dosage do not result in further antitumor activity. In patients, it is not known whether this plateau has been reached when the maximal tolerated dose has been given.

For many effective anticancer agents, myelotoxicity is the major toxicity that limits further drug administration. Recent improvements in supportive care, the development of hematopoietic growth factors, and the use of bone marrow and stem cell support now allow for the safer administration of higher doses of chemotherapeutic agents. The question remains, however, whether increasing the dose intensity of chemotherapy will result in improved clinical outcome.

The Dose-Intensity Concept

Several retrospective analyses in breast cancer have suggested that dose might correlate with clinical outcome. In 1981, Bonadonna and Valagussa[5] reported that women with node-positive breast cancer who received > 85% of a planned dose of CMF (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil [5-FU]) achieved a better clinical outcome than those who received less. On the other hand, those who received < 65% of the intended dose fared no better than women in the untreated control group. Based on information from this trial as well as other retrospective studies, Hryniuk et al devised the concept of "dose intensity," a measure of the amount of drug administered per unit time. Retrospective evaluations of dose intensity vs outcome in both the adjuvant and metastatic disease settings supported the hypothesis that higher doses of chemotherapy impart a better outcome in breast cancer. These results led to a series of prospective, randomized clinical trials that addressed the issue of dose in breast cancer.[6,7]

Dose Escalation in the Subtransplant Range

Several methods are used to increase the dose of drug delivered. Biganzoli and Piccart summarized a number of variables in breast cancer treatment, including dose intensity, dose density, cumulative dose delivered, and duration of therapy, that may contribute to treatment results.[8] They postulated the existence of at least five models using these variables that could permit the delivery of higher chemotherapy doses in both early and advanced stages of breast cancer. Many of these have been tested in the randomized clinical trials discussed in this article. In general, these trials have sought to evaluate the effect of dose increases of anthracyclines (such as doxorubicin or epirubicin [Ellence]), alkylating agents (such as cyclophosphamide), and more recently, the taxanes.

Dose Escalation in Advanced Breast Cancer
Low-Dose vs Standard-Dose CMF: In one of the first trials to evaluate the effect of drug dose on response, Tannock et al prospectively compared two doses of CMF in patients with previously untreated metastatic breast cancer.[9] Low-dose CMF (cyclophosphamide, 300 mg/m²; methotrexate, 20 mg/m²; and 5-FU, 300 mg/m² IV, on day 1 of 21-day cycles) was compared to standard-dose CMF (600, 40, and 600 mg/m², respectively). Response rates were 26% for the standard-dose arm and 11% for the low-dose arm, demonstrating that low-dose CMF was inferior to standard dosing. Median survival was 15.6 months in the standard-dose arm and 12.8 months in the low-dose arm—a difference that was not significant. The European Organization for Research and Treatment of Cancer compared a standard CMF regimen that incorporated higher oral doses of cyclophosphamide and a higher 5-FU dose with a modified lower-dose IV schedule. Results showed improvements in both response and survival with the higher-dose intensity standard CMF regimen.[10]

High-Dose Epirubicin: In the past decade, eight large randomized trials have examined the effects of epirubicin dose on outcome for women with advanced, metastatic breast cancer.[11-18] These trials evaluated epirubicin alone or in combination with cyclophosphamide, 5-FU, or both (FEC). The increased dose intensity of epirubicin in these trials ranged from approximately 1.5- to 3.5-fold, and the planned and delivered dose intensities were generally similar.

In all of these studies, increased dose intensity was associated with improved response rate. In some trials, this was associated with a prolongation in median time to progression. However, none of these trials noted any significant survival benefit. One consistent finding supported the concept of a dose threshold; ie, that clinical outcome as measured by response rate is compromised by a low epirubicin dose intensity. However, there is little evidence for a substantial benefit of epirubicin dose escalation beyond the standard dose.

High-Dose Paclitaxel: More recently, paclitaxel (Taxol) has emerged as an effective agent for the treatment of breast cancer. Nabholtz et al compared the doses of paclitaxel, 175 mg/m² vs 135 mg/m², both given as a 3-hour infusion every 21 days to 471 patients with metastatic breast cancer.[19] Results showed a trend toward a better overall response rate (29% vs 22%) and complete response rate (5% vs 2%), as well as a significant improvement in median time to disease progression (4.2 vs 3 months, \( P = .027 \)) for the higher dose. However, median survival and response duration were not affected by dose.

Examining even higher doses of paclitaxel, a Cancer and Leukemia Group B (CALGB) trial randomized 475 women with stage IV breast cancer to paclitaxel doses of 175, 210, or 250 mg/m², all infused over 3 hours.[20] Response rates were similar for the three dosing schedules (21%, 28%, and 22%, respectively), as were median survival rates (9.8, 11.8, and 11.9, months, respectively). A correlation of borderline significance \( (P = .03) \) between paclitaxel dose and time to treatment failure (3.8, 4.1, and 4.8 months for 175, 210, and 250 mg/m², respectively) was observed. Neurosensory and hematologic toxicities were found to increase with the dose of paclitaxel. Thus, based on these trials, there is no obvious benefit for the routine dose escalation of paclitaxel beyond the dose of 175 mg/m² over 3 hours.

Dose Escalation in Adjuvant Therapy for Early-Stage Breast Cancer

It may be argued that improved outcome with increased dose intensity will most likely be seen in the adjuvant setting, where the target is micrometastatic disease. One of the most important trials to examine the role of anthracycline and alkylating agent dose intensity was CALGB 8541.[21] Women with node-positive breast cancer were randomly assigned to receive cyclophosphamide, doxorubicin, and 5-FU at one of the following three levels of dose intensity: high dose (600 mg/m² cyclophosphamide, 60 mg/m² doxorubicin, and 600 mg/m² 5-FU, every 4 weeks for four cycles); moderate dose (400 mg/m² cyclophosphamide, 40 mg/m² doxorubicin, and 400 mg/m² 5-FU, every 4 weeks for six cycles); or low dose (300 mg/m² cyclophosphamide, 30 mg/m² doxorubicin, and 300 mg/m² 5-FU, every 4 weeks for four cycles). On day 8 of each cycle, 5-FU was repeated. Cumulative doses of the three drugs were identical in the high- and moderate-dose groups and 50% lower in the low-dose group. Thus, the high- and moderate-dose arms featured the same cumulative dose with different dose intensities, whereas the low-dose arm had both reduced cumulative doses and
reduced dose intensities.

In the first report of this study, the low-dose arm showed poorer results in all clinical outcomes at 3 years when compared with the moderate- or high-dose arms. However, no major differences were noted between outcome in the moderate- and high-dose arms. Disease-free survival at 3 years was 74%, 70%, and 63%, while overall survival was 92%, 90%, and 84% for the high-, moderate-, and low-dose arms, respectively. Updated results after a median follow-up of 9 years continue to show benefit for the moderate- and high-dose arms compared with the low-dose group, with no substantial difference in outcome between the first two arms.[22] Disease-free survival at 5 years was 66%, 61%, and 56%, while overall survival was 79%, 77%, and 72% for the high-, moderate-, and low-dose arms, respectively.

A provocative finding from this trial was the retrospective observation that high expression levels of the HER2/neu gene were associated with superior patient outcome on the high-dose arm.[23] Analyses of tumors derived from 397 patients enrolled in CALGB 8541 demonstrated that patients assigned to the high-dose, but not the low- or moderate-dose, had significantly longer disease-free survival and overall survival if their tumors had high levels of expression of the HER2/neu protein. However, a second analysis that included a further 595 patients was not as compelling,[24] and thus, the issue of HER2/neu overexpression as a predictor of chemotherapy dose response remains an open question.

A similarly designed trial was reported by the French Adjuvant Study Group.[25] Over 500 women with high-risk, node-positive breast cancer were randomized to receive six cycles of FEC 50 (fluorouracil, 500 mg/m²; epirubicin, 50 mg/m²; and cyclophosphamide, 500 mg/m², on day 1 every 3 weeks) or the same regimen with epirubicin, 100 mg/m² (FEC 100). As expected, toxicity was less in the FEC 50 group, but clinical outcome was also inferior. Disease-free survival at 5 years was 54.8% for FEC 50 and 66.3% for FEC 100 (P = .03), while 5-year overall survival was 65.3% for FEC 50 and 77.4% for FEC 100 (P = .007). Taken together, the results of these two trials are consistent with a dose threshold hypothesis; that is, an adequate dose of chemotherapy is necessary to maximize efficacy. However, neither trial addresses the role of routine dose escalation of these agents beyond standard doses.

**High-Dose Cyclophosphamide:** Dose escalation of cyclophosphamide with fixed-dose doxorubicin has now been tested in two sequential National Surgical Adjuvant Breast and Bowel Project (NSABP) trials as adjuvant treatment in women with node-positive breast cancer.[26,27] In both trials, doxorubicin at 60 mg/m² was given every 3 weeks for a total of four cycles, while the cyclophosphamide dose varied. In NSABP B-22, patients in the standard-dose arm received 600 mg/m² of cyclophosphamide in each cycle, whereas patients in the high-dose arm received 1,200 mg/m² of cyclophosphamide in each of the four cycles.[26] An intermediate arm administered 1,200 mg/m² of cyclophosphamide during the first two cycles only, thus providing the same total cyclophosphamide dose as in the standard-dose arm, but at a higher dose intensity since it was administered over half the time. Colony-stimulating factors were not used. Over 2,300 patients were randomized in this trial.

Results showed no significant differences in disease-free or overall survival through 5 years. The 5-year disease-free survival rates were 62%, 60%, and 64% for the standard-, intermediate-, and high-dose arms, respectively, while overall survival rates were 78%, 77%, and 77%. Not surprisingly, toxicities worsened with treatment intensity. Of particular concern was the observation of hematologic malignancies in two patients in the standard-dose group, one patient in the intermediate-dose group, and three patients in the high-dose group. Thus, in this trial, the administration of cyclophosphamide at a twofold higher dose intensity offered no benefit and was associated with excess toxicity.

Before the results of NSABP B-22 were reported, NSABP B-25 explored the value of even greater cyclophosphamide dose escalation, again with fixed-dose doxorubicin.[27] In this study, 2,548 node-positive patients were randomized to receive four cycles of variable doses of cyclophosphamide with doxorubicin at 60 mg/m²/cycle. The three cyclophosphamide levels were 1,200 mg/m²/cycle for four cycles; 2,400 mg/m²/cycle for two cycles; and 2,400 mg/m²/cycle for four cycles. Granulocyte colony-stimulating factor (G-CSF [Neupogen]) was routinely administered.
Dose Intensity for Breast Cancer
Published on Physicians Practice (http://www.physicianspractice.com)

beginning on day 2.

This trial did not show any statistically significant benefit of cyclophosphamide doses increased fourfold over the standard dose. At 5 years, the disease-free survival of women in the three groups, respectively, was 60%, 61%, and 66%—a difference that did not achieve statistical significance. Survival was identical across the three groups at 77%, 76%, and 78%. Of note, 14 patients enrolled in this trial have developed acute myelogenous leukemia and 7 other patients were found to have myelodysplastic syndrome—a 0.8% incidence of these myeloproliferative disorders.

Based on the combined results of NSABP B-22 and B-25 to date, dose escalation of cyclophosphamide beyond standard dose in this type of outpatient regimen is not a useful clinical strategy and is clearly associated with greater toxicity.

**High-Dose Doxorubicin:** Doxorubicin is an active agent in breast cancer, and studies of its use as a single agent in metastatic breast cancer suggest a dose-response relationship. Based on these observations, the CALGB instituted a trial investigating escalating doses of doxorubicin in the adjuvant setting.[28] This Intergroup trial, CALGB 9344, randomized 3,120 women with node-positive breast cancer in a 3 × 2 factorial trial design to a standard dose of cyclophosphamide (600 mg/m²) plus doxorubicin (60, 75, or 90 mg/m²) given every 3 weeks for a total of four cycles, followed or not by paclitaxel at 175 mg/m² every 3 weeks for four cycles. Use of G-CSF prophylaxis was allowed for the intermediate dose of doxorubicin and was required for the highest dose. Disease-free survival at 18 months was 86% in doxorubicin/cyclophosphamide recipients not given paclitaxel and 90% in those who were given paclitaxel; overall survival was 95% and 97% in the two groups, respectively. No effect was noted with changes in the doxorubicin dose. Thus, initial results of this trial would argue that a 50% increase in doxorubicin dose is not beneficial in the adjuvant treatment of node-positive breast cancer. Results from this series of trials are summarized in Table 1.

**Dose Escalation in the Transplant Range**

The administration of single or repeated high-dose chemotherapy with stem cell or bone marrow rescue represents the ultimate expression of dose intensification. Early phase I and II trials of high-dose chemotherapy used high doses of alkylating agents in patients with advanced, resistant breast cancer.[29] Responses were noted even in some heavily pretreated patients, but enthusiasm for this treatment was tempered by the substantial toxicities experienced by these patients and early relapse in most patients. However, the activity of this modality in heavily pretreated patients prompted the evaluation of high-dose therapy with stem cell support in patients with lower-volume disease and earlier stages of breast cancer.

As a consequence of the high incidence of breast cancer and great enthusiasm for this approach, breast cancer became one of the most common indications for autologous transplantation in the United States.[30] On the following pages, we report the results of randomized phase III trials comparing high-dose chemotherapy with conventional therapy in patients with metastatic or high-risk primary breast cancer. These results are summarized in Table 2.

**High-Dose Therapy/Transplantation in Advanced Breast Cancer**

To date, five randomized trials of high-dose chemotherapy with bone marrow or stem cell transplantation have been reported in advanced breast cancer, four of which are summarized in Table 2. The first was reported in 1995 by Bezwoda et al from the University of Witwatersrand in South Africa.[31,32] Although this study showed promising results, the investigator ultimately admitted to fraud after review of a separate trial of high-dose therapy in patients with high-risk primary breast cancer.[33] The study in metastatic patients has been formally reviewed, and the reviewers were unable to verify the reported data.[34]

**PEGASE Study:** In a small study of high-dose therapy in metastatic breast cancer, the French PEGASE (Programme d’Étude de la Greffe Autologue dans les Cancers du Sein) 04 study randomized 61 patients who had responded to four to six cycles of conventional chemotherapy to either continuation of the same therapy (29 patients) or treatment with a high-dose regimen of
mitoxantrone (Novantrone), cyclophosphamide, and melphalan (Alkeran) with stem cell support (32 patients).[35] Significant improvement was noted for the high-dose arm in median progression-free survival (27 vs 16 months) and 2-year relapse rate (27% vs 52%). In addition, there was a trend in improvement in median overall survival for the high-dose arm (36 vs 16 months) that was not statistically significant. Thus, this small trial does provide promising results.

Philadelphia Bone Marrow Transplant Group: In a large randomized study by the Philadelphia Bone Marrow Transplant Group, women with newly diagnosed stage IV breast cancer who received induction chemotherapy with CAF (cyclophosphamide, Adriamycin, 5-FU) or CMF and achieved a complete or partial response were randomly assigned to continuation of CMF for up to 2 years or the STAMP V regimen (Solid Tumor Autologous Marrow Program, ie, high-dose chemotherapy with cyclophosphamide, carboptatin [Paraplatin], and thiopeta [Thioplex], plus autologous bone marrow and/or stem cell support).[36]

A total of 553 women received four to six cycles of induction therapy and 310 achieved a response (partial response in 252 women; complete response in 58 women). Of these responding patients, 110 were randomized to the high-dose arm and 89 to the conventional-dose arm. Fifteen patients were found to be ineligible, and thus, 184 of the 199 patients were included in the primary analysis. A total of 101 patients entered the high-dose arm; 83 in the maintenance CMF arm. Of the 184 patients, 20 (11%) did not adhere to their randomization assignment (6 of 101 [6%] in the high-dose arm and 14 of 83 [17%] in the CMF arm).

With a median follow-up of 37 months, no significant differences between the high-dose and CMF arms were seen in 3-year overall survival (32% vs 38%, respectively) or median survival (24 vs 26 months, respectively). In addition, this study did not demonstrate a major difference between the two groups in time to progression, progression-free survival, or treatment-related mortality. This trial has been widely criticized due to the small fraction of enrolled patients who were actually randomized. However, it represents the largest randomized trial of a transplant strategy vs a conventional approach in metastatic breast cancer.

Duke Crossover Study: In a crossover study at Duke University, 98 patients with metastatic breast cancer who achieved a complete response with initial induction chemotherapy with AFM (Adriamycin, 5-FU, methotrexate) were randomly assigned to initial observation, with immediate transplant or transplant at the time of relapse.[37] The STAMP I alkylator regimen of cyclophosphamide, carmustine (BiCNU), and cisplatin (Platinol) was employed in both arms of the trial. Median follow-up for patients is now about 5 years. Not surprisingly, the median disease-free survival for patients who underwent high-dose therapy at first remission was 14 months, whereas it was only 4 months for patients who were observed after the first complete response. Thus, high-dose therapy apparently results in improved disease-free survival, compared with observation. Paradoxically, overall survival in this trial was better for women who underwent high-dose therapy at second relapse. Median survival was 2.3 years for patients who underwent high-dose therapy at the time of their first complete response and 3.2 years for patients who received transplant at the time of their second recurrence. This is a provocative finding, but one of uncertain significance.

Duke Study of Immediate vs Delayed Transplant: In a separate study, investigators from Duke examined the role of immediate vs delayed transplant after standard-dose chemotherapy for patients with metastatic disease to the bone only.[38] A total of 85 patients with hormone-refractory or hormone-insensitive breast cancer were treated with a maximum of four cycles of AFM followed by restaging. Patients who did not progress were then randomized to observation or to immediate high-dose consolidation with the STAMP I regimen followed by progenitor cell support. Patients in the observation arm received the same high-dose therapy at disease progression. All sites of bony disease were irradiated after high-dose therapy (in patients randomized to the immediate high-dose arm) or at randomization to observation. Of the 85 patients enrolled, 69 were randomized[35 to immediate high-dose therapy and 34 to observation.

All patients randomized to observation showed disease progression, and 66 of the 69 randomized patients received high-dose therapy. At a median follow-up of 4.9 years, patients treated with initial high-dose therapy had a median overall survival of 2.01 years and progression-free survival of 0.91 years. For patients in the observation arm, median overall survival was 1.8 years and
Dose Intensity for Breast Cancer
Published on Physicians Practice (http://www.physicianspractice.com)

progression-free survival was 1.0 years. The difference in the progression-free survival for these two arms is statistically significant ($P < .0001$). Six patients in the immediate-transplant arm remain progression free, compared to three in the delayed-transplant arm.

High-Dose Therapy/Transplantation in Early-Stage Breast Cancer

Six randomized trials of high-dose chemotherapy in patients with high-risk localized breast cancer have been reported, five of which are summarized in Table 2.

Dutch Pilot Study: In a small study from the Netherlands, 97 patients with a positive infraclavicular lymph node biopsy at diagnosis of breast cancer were treated with three courses of preoperative FEC.[39] Responding patients were subsequently randomized and underwent definitive surgical therapy, a fourth course of FEC chemotherapy, and treatment with radiation and tamoxifen (Nolvadex). In addition, half of these responding patients also received high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin, with stem cell support after the final course of FEC. A total of 81 patients were randomized; however, only 35 of the 41 patients who had been assigned to high-dose chemotherapy actually received the intended therapy. At a median follow-up of 49 months, the 4-year overall and relapse-free survival rates for all 97 patients entered into the trial were 75% and 54%, respectively. No difference has been observed in progression-free or overall survival between the two arms. This trial was a pilot study to assess the feasibility of this approach; its statistical power was limited and did not provide sufficient power to exclude a reduction in odds of relapse of up to 40%.

Large Dutch Trial: In a subsequent Dutch study, Rodenhuis and colleagues treated 885 patients with stage II or III breast cancer and four or more positive axillary lymph nodes with FEC followed by radiation and tamoxifen. Patients were randomized to receive either five courses of FEC or four courses of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin, with stem cell transplantation in place of the fifth cycle of FEC.[40] At a planned subgroup analysis of the first 284 patients, those in the high-dose therapy arm achieved a benefit in 3-year overall survival and relapse-free survival. There was a reduction in the odds of relapse of 0.20 ($P = .009$) and a 10% improvement in overall survival in favor of the high-dose therapy arm. Given that this is the largest trial to date in patients with localized breast cancer, these early results are promising. Full results for the entire group are expected in 2002.

M. D. Anderson Trial: Hortobagyi et al have reported the results of an M. D. Anderson Cancer Center trial in which 78 patients with 10 or more axillary nodes at initial surgery or 4 or more positive nodes after primary chemotherapy received eight cycles of FAC (5-FU, Adriamycin, cyclophosphamide) with or without two courses of high-dose therapy with cisplatin, etoposide, and cyclophosphamide, with stem cell support.[41] Tamoxifen was planned for postmenopausal patients with estrogen receptor-positive tumors, and chest wall radiotherapy was planned for all patients. After a median follow-up of 6.5 years, there was no evidence of improved outcome for patients treated in the high-dose arm. Again, because of the trial’s small size, this trial cannot rule out a 30% difference in survival between the treatment arms.

Scandinavian Breast Cancer Study Group: The Scandinavian Breast Cancer Study Group 9401 trial was a population-based study of nine cycles of FEC at doses tailored to individual hematologic tolerance vs three cycles of FEC followed by STAMP V with autologous hematopoietic support.[42] Participants were selected because their 5-year risk of relapse was at least 70%, based on Scandinavian databases. Over half of the eligible patients participated, making this the most representative of the high-dose trials to date. The planned cumulative dosing for the tailored arm was actually higher than that of the high-dose arm. With a median follow-up of 34.3 months, the 3-year relapse-free survival rate was 72% for patients in the tailored FEC group compared with 63% for patients in the high-dose arm ($P = .04$), while the 3-year overall survival rate was 83% for patients in the tailored FEC group compared with 77% for patients in the high-dose arm ($P = .12$). Higher incidences of acute myelogenous leukemia and myelodysplastic syndrome were seen in the women who had received tailored FEC.

CALGB Trial: In CALGB study 9082, women with 10 or more involved axillary lymph nodes received four cycles of CAF and were subsequently randomized to either high-dose or intermediate-dose
STAMP I—a regimen that requires G-CSF but not stem cell support.[43] With a median follow-up of 5.1 years, event-free survival rates for the 783 randomized women were 61% for high-dose chemotherapy and 60% for intermediate-dose chemotherapy. Survival was similar at 70% and 72% for high- and intermediate-dose chemotherapy, respectively. Although fewer relapses were observed in the high-dose arm, there were 32 treatment-related deaths in the high-dose arm and none in the intermediate-dose arm.

Other Trials: Initial reports from a small study in South Africa were strikingly positive.[44] However, review of this study has documented fraud on the part of the investigator, leading to retraction of the data.[33] Thus, this study is not included in this review or in Table 2. The Eastern Cooperative Oncology Group recently completed accrual of a large randomized trial with over 400 patients (E2190), but results of this trial have not yet been reported.

Future Directions of Dose-Intensive Therapy in Breast Cancer

It is clear that the use of high-dose chemotherapy has profound effects on the immune system. In particular, immune reconstitution after high-dose marrow-ablative chemotherapy is associated with transient alterations in immune surveillance, immune recognition, and immune responses.

In animal models, the antitumor effect of high-dose chemotherapy can be improved severalfold by the use of immune-modulating cytokines.[45] Considerable data show that the effectiveness of immune-directed therapies is enhanced when they are combined with cytotoxic agents.[46] The exact mechanism by which chemotherapeutic agents augment antitumor immunity is unknown, but may be related to shifts in tumor cytokines favoring the generation of cytotoxic lymphocytes, the key effector cells that mediate tumor-specific lysis.[47]

It has also been shown that levels of circulating tumor cell antigens are elevated after high-dose chemotherapy and that patients are able to mount an antigen-specific immunologic response to vaccination after high-dose therapy. Furthermore, the antitumor effect of high-dose chemotherapy, even if incomplete, allows for the use of immune modulation in a setting of minimal tumor burden, where such therapy is most likely to be beneficial.[48] Based on these observations, a significant body of ongoing research in transplantation is examining the potential means of inducing an immune antitumor response. These include the use of nonmyeloablative, allogeneic transplants (minitransplants) with or without donor lymphocyte infusions; whole modified tumor cell vaccines; and vaccination with known tumor-specific antigens.

Dose Density

Hudis et al have shown that breast cancer may most closely fit a Gompertzian model of growth.[49] In this model, smaller tumors grow faster, and thus tumor regrowth between treatment cycles is most rapid when cell kill is greatest. By decreasing the time between treatments, the time available for tumor regrowth is reduced. This approach, which has been termed "dose density," utilizes the sequential administration of single agents in an intensive fashion rather than in combination. Benefits of a dose-dense treatment approach include the ability to easily incorporate newer agents, such as the taxanes, into treatment plans. Clinical data in support of this approach were derived indirectly from a trial by the Milan Cancer Institute, which showed superior outcomes in women with more than three positive axillary nodes who were treated with four cycles of doxorubicin followed by eight cycles of CMF, as opposed to alternating doxorubicin and CMF.[50]

The concept of dose density is undergoing prospective evaluation in Intergroup studies in the United States. In one trial, S9313, women with high-risk, node-negative or one to three node-positive breast cancer are being randomized to six cycles of doxorubicin and cyclophosphamide in combination vs a sequence of doxorubicin followed by cyclophosphamide. The duration and cumulative chemotherapy dose are identical in both arms. The design of this trial will allow for the examination of both sequence and dose density.

A second trial, C9741, is a four-arm trial of doxorubicin/cyclophosphamide followed by paclitaxel vs doxorubicin followed by paclitaxel followed by cyclophosphamide, administered to node-positive
women at 2- to 3-week intervals. Finally, a third Intergroup trial was testing the relative value of a
dose-dense approach similar to that just described (doxorubicin followed by paclitaxel followed by
cyclophosphamide), with a strategy that includes high-dose chemotherapy with autologous stem cell
support. This trial, however, was closed due to poor accrual.

**Summation Dose Intensity**

Hryniuk and colleagues have recently postulated that the magnitude of a dose-intensity effect in
breast cancer might be better defined by applying the concept of "summation dose
intensity,"[51,52] which integrates the therapeutic contribution of individual agents within a
combination regimen. Compared to Hryniuk's original relative dose-intensity method,[6,7]
summation dose intensity requires a more detailed knowledge of the dose-response characteristics
of each drug. A summation dose-intensity scale has been used to retrospectively evaluate
treatments in breast cancer and may be used prospectively to guide dosage increases beyond the
conventional range.

**Conclusions**

Despite nearly 2 decades of study, the hypothesis that increasing chemotherapy doses above
standard levels will positively affect clinical outcome in breast cancer remains unproven. The
benefits of increased doses that have been observed in preclinical models of breast cancer and other
malignancies have not been clinically evident in breast cancer. In the metastatic setting, a higher
dosage sometimes results in increased responses, but these responses seldom translate into
increased time to progression and, in general, do not affect survival.

Evidence from the randomized trials presented in this article supports the concept of a threshold
effect, thereby indicating that underdosing of active agents is associated with poorer clinical
outcome. However, escalation of dosage is associated with higher costs, increased toxicities, and
adverse effects on quality of life. Until these risks are outweighed by consistently documented
benefits in outcome, such as improved survival or increased cure rate, the routine use of dose
escalation outside of clinical trials is not warranted.

Likewise, although early data are provocative, approaches using high-dose chemotherapy with
autologous bone marrow or stem cell support for breast cancer, these approaches should be
considered investigational, and thus, only appropriate in the setting of a clinical trial. To date,
randomized trials of autologous transplant have provided ambiguous results in both adjuvant and
metastatic settings. It is hoped that longer follow-up of these trials, as well as the emergence of
results from other ongoing or completed trials, will provide more definitive information. In the
interim, enthusiasm for this technology should be tempered by the absence of clear data from
clinical trials that establish any superiority of this approach.

**References:**


38. Madan B, Broadwater B, Rubin P, et al: Improved survival with consolidation high-dose cyclophosphamide, cisplatin and carmustine (HD-CPB) compared with observation in women with...


