Drugs 2004; 64 (17): 1851-1860
0012-6667/04/0017-1851/$34.00/0



# High-Dose Chemotherapy in Breast Cancer

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## Abstract

High-dose chemotherapy is based on the scientific hypothesis that escalating the dose of drug will overcome drug resistance and improve outcome. Autologous bone marrow transplantation and, more recently, peripheral stem cell transplantation used as a means to restore marrow, made this a viable treatment for patients with selected tumours such as haematological malignancies. The role in breast cancer is less certain.

Given the known as well as the potential toxicities, the objective of high-dose chemotherapy should be cure as opposed to palliation. However, the natural history of breast cancer can be protracted, with relapses occurring 15–20 years after treatment or within months of curative surgery. In breast cancer there is a positive correlation between recurrence-free and long-term survival. Therefore, the recurrence-free survival can be considered a surrogate endpoint in clinical trials. In patients with metastatic disease where cure is rare, at best, duration of a disease-free state may be a surrogate for overall benefit. Alternatively, time to progression may be another endpoint in the evaluation of treatment for metastatic disease. This is based on the assumption that quality of life is enhanced without progression of disease.

Toxicity is the significant issue in the use of high-dose chemotherapy. The most common toxicity is myeloablation, potentially requiring prolonged hospitalisation. The only justification for these toxicities would be evidence of significant and meaningful benefit. A clinically relevant benefit with high-dose chemotherapy has not been seen in major randomised clinical trials of breast cancer in both the adjuvant and metastatic setting. In patients with advanced breast cancer, a small percentage may achieve long-term, disease-free survival, although there is no improvement in overall survival.

Nonetheless, some investigators believe that high-dose chemotherapy holds promise, although currently this treatment is not recommended outside of a well designed prospective trial. These studies have provided useful information regarding cancer treatment. However, ongoing study of drug administration intervals, that is, dose-dense therapies, may lead to an approach that allows superior and less toxic treatment for breast cancer.

High-dose chemotherapy is predicated on the assumption that increased acute drug exposure will result in improved antitumour efficacy. Maximal dose escalation was found to be limited by the

development of bone marrow suppression that led to the field of transplantation, which initially utilised bone marrow but later peripheral blood stem cells. The underpinning for the entire field of endeavour is the scientific hypothesis that for certain drugs, most commonly alkylating agents, escalating the dose will overcome drug resistance, increase cell kill and, therefore, improve outcome.[1] The technique of autologous bone marrow transplantation and, recently, peripheral stem cell transplantation as a means of restoring the marrow, made high-dose chemotherapy a viable and attractive treatment possibility for patients with selected malignancies including breast cancer. It has proved successful in the treatment of haematological malignancies (leukaemia and lymphoma), which are known to be chemosensitive, but a role in breast cancer has not been established.[2]

There are two settings in which high-dose chemotherapy approach has been tested. The first is the advanced disease setting, comprising locally advanced or metastatic breast cancer, and the second is as an adjuvant to surgery and radiotherapy for earlier stage breast cancer, generally with significant ipsilateral nodal involvement. In both settings, the general approach has been similar, comprising (with some exceptions) a conventional chemotherapy phase followed by the delivery of one or several cycles of high-dose chemotherapy supported by reinfusion of bone marrow or peripheral blood stem cells.

The rationale for this approach in breast cancer has previously been reported.[3] Typically, an initial course of conventional drugs such as an anthracycline-based combination (i.e. cyclophosphamide, doxorubicin and fluorouracil) is administered as 'induction' treatment, followed by high-dose consolidation. Usually, upon completion of the initial treatment phase and in the advanced disease setting the demonstration of chemosensitive disease based upon evidence of response (partial or complete), one or more courses of high-dose treatment is delivered.[1] The theoretical basis for induction treatment is based on the predictions of the Skipper-Schabel model of log-kill.[1,4] This model predicts that several cycles of effective chemotherapy can reduce the tumour burden substantially, on the basis of fractional cell-kill leaving a smaller population of cells that may or may not be resistant but that can be eliminated with subsequent high-dose treatment. The Gompertzian model of tumour growth supports this hypothesis by predicting that a smaller volume of tumour cells, which have a relatively increased growth fraction, will have a greater sensitivity to cell-cycle-specific agents.[1,5] From this, one can predict that high-dose chemotherapy could be most effective when given at the time of minimal tumour burden. However, the hypothesis has recently been challenged by several randomised clinical trials (discussed in section 1).

Two seminal studies *in vivo* supported the conclusion that dose escalation, albeit using non-myeloablative doses of drugs in combination, could be valuable. In a 20-year follow-up of cyclophosphamide, methotrexate, fluorouracil (CMF), Bonadonna et al.[3] noted a longer disease-free survival in a group of patients receiving a higher percentage of the intended treatment dose. In a prospective randomised trial, Wood et al.[6] likewise reported that women receiving either high or moderate doses of cyclophosphamide, doxorubicin (adriamycin) and fluorouracil (CAF) had significant improvement in disease-free as well as overall survival compared with those receiving lower doses.[6] Although these results did not involve myeloablative dose ranges, the data along with laboratory findings were seen as justification for a variety of clinical trials in both the adjuvant and metastatic settings for breast cancer during the 1980s and 1990s.[7-12] In 1989, 7% of the high-dose treatments in the US were delivered as adjuvant treatment for high-risk breast cancer. By 1995, 49% of all high-dose treatments reported to the Autologous Bone Marrow Transplant Registry (ABMTR) were for breast cancer,[13,14] which included a much smaller percentage of patients with stage IV disease. In spite of 4503 autologous bone marrow transplants performed for early disease in 1994 and 1995, and this number increasing to 5695 as indicated by partial data from 1996 and 1997,[2] a benefit for high-dose chemotherapy remains unproven. Initial enthusiasm

for this procedure has been tempered by a lack of demonstrated advantage in any of the prospective randomised trials reported thus far, as well as by scientific misconduct involving two South African clinical trials.[1,15] This decline in enthusiasm was clearly documented by van Amerongen who reported an abrupt decline in requests for autologous bone marrow transplantation for metastatic breast cancer following the presentation of pivotal randomised trials.[16] Furthermore, randomised trials in both the adjuvant and metastatic settings have not been designed to precisely address the same scientific questions, making potential comparisons or meta-analysis challenging.

Given its known and potential toxicities, the objective of high-dose chemotherapy should be cure as opposed to palliation, although it is not impossible that a successful high-dose approach could result in significant long-term palliation and time without treatment as compared with conventional chemotherapy.[17] The natural history of breast cancer can be protracted. Relapse can be seen within months of seemingly curative surgery, or the disease may recur as long as 15–20 years after treatment; only properly conducted prospective randomised trials with long follow-up can adequately address the role of an experimental approach.[17] In the short run, determination of true cure is perhaps not a practical endpoint, even when evaluating primary therapy. At the same time, there is a positive correlation in breast cancer between recurrence-free and long-term survival such that this intermediate endpoint might be a surrogate for overall survival and benefit.[17,18] In patients with metastatic disease, cure is rare at best; however, if a disease-free state is obtained, as in early-stage disease, its duration could be a surrogate for overall benefit. Another endpoint in the evaluation of treatment for metastatic disease might be simply time to disease progression, based on the assumption that quality of life is enhanced in the absence of such progression. In any case, cure or prolonged survival with high quality of life is the appropriate goal of therapy, and the more toxic the treatment, the greater the benefit needed to justify it.

Toxicity is the most significant issue in the use of high-dose chemotherapy, and the most obvious toxicity is myeloablation, requiring prolonged hospitalisation or long stays in outpatient/onsite facilities. Life-threatening acute or chronic toxicity, such as pneumonitis, has been described. Patients experience significant fatigue, gastrointestinal symptoms often requiring parenteral nutrition, and skin abnormalities. As an example, in the early analysis of the Cancer and Leukemia Group B (CALGB) 9082/Intergroup adjuvant trial, Peters et al.[10] reported 7.4% mortality, mostly due to carmustine pneumonitis. In addition, there was increased mortality in centres that performed fewer than 50 autologous bone marrow transplants annually.[10] Other toxicities that have been described include veno-occlusive disease associated with multiple courses of high-dose chemotherapy, and long-lasting sensory and ototoxicity in association with cisplatin or carboplatin regimens.[17]

Other important and common chronic toxicities include premature menopause and its sequelae, chronic fatigue, cardiac dysfunction and renal impairment. In addition, second malignancies have been well documented, including myelodysplastic syndrome (most common), leukaemia and also solid tumours.[17,19,20] The only justification for these toxicities would be evidence of significant and meaningful benefit. Following sections discuss the results of major randomised trials of high-dose chemotherapy in adjuvant setting and metastatic breast cancer.

## 1. Randomised Clinical Trials (RCTs) of High-Dose Chemotherapy in the Adjuvant Setting

High-dose chemotherapy in the adjuvant setting for ‘high-risk’ breast cancer became a common approach in both the academic and community settings during the 1990s. Early studies that fuelled this use included patients who presented with ten or more positive nodes and, later, four or more positive nodes. Some studies included patients whose tumours were inflammatory at presentation or exceeded 5cm maximum diameter. The rationale for high-dose chemotherapy in the adjuvant setting fo-

cused on two issues. First, the tumour burden (which is minimal at this time in comparison with metastatic disease) might favour a curative benefit. Secondly, phase II studies suggested marked improvements compared with historical results. In addition, some investigators theorised that drug resistance would be minimal or at least less in the 'early' adjuvant setting as opposed to the metastatic setting. Patients with minimal prior treatment and minimal tumour burden were presumed to be more tolerant of high-dose chemotherapy, as they are generally healthy and have a maximal performance status as compared with those with advanced or recurrent disease. The first randomised data were provided by two small, single-institution studies in the adjuvant setting, one from the Netherlands Cancer Institute (Amsterdam, The Netherlands) published in 1998[8] and the other from MD Anderson Cancer Center (Houston, TX, USA).[9] Both studies have been criticised for many reasons, including delay between conventional induction and high-dose chemotherapy, not being powered to detect a difference in survival and, in the MD Anderson Cancer Center trial, for using chemotherapy doses that did not actually require a haematopoietic stem cell transplant.[21] However, inconsistent with the earlier studies testing dose escalation in the conventional dose range, neither of these studies suggested a significant advantage for high-dose chemotherapy.

Several larger randomised trials were reported at the 1999 Americal Society of Clinical Oncology (ASCO) annual meeting. Peters et al.[10] presented preliminary results of the CALGB 9082/Intergroup trial in which 783 patients with ten or more involved nodes were randomised to receive conventional CAF as induction therapy followed by either a high-dose cyclophosphamide, cisplatin, and carmustine (BCNU) [CPB] regimen or by an intermediate-dose CPB regimen. The latter did not require haematopoietic stem cell support. At the time of the report, no event-free or overall survival differences were noted between the two arms. However, there were fewer relapses in the high-dose group coupled with an excess early death rate of 7.4%.[10]

At the same ASCO meeting, a 525 patient Scandinavian study was presented[11] and has subsequently been published.[22] These patients were randomised to nine courses of fluorouracil, epirubicin and cyclophosphamide (FEC) plus granulocyte colony-stimulating factor (G-CSF) and antibacterials – with doses tailored in response to the toxicity of the previous cycle – or three courses of FEC (two for induction, one for stem cell mobilisation) followed by a high-dose cyclophosphamide, thiotepa and carboplatin (CTCb) regimen.[22] There was an event-free survival advantage for the FEC alone arm. In the analysis of drug doses, those treated with the FEC regimen for nine cycles actually received a higher median total dose of epirubicin at 780 mg/m$^2$ in contrast with 181 mg/m$^2$ in the CTCb group, suggesting that drug exposure for FEC may be important. This finding is further supported by the CALGB trial (8541) reported by Wood et al.[6] testing CAF in patients with node-positive breast cancer. These investigators demonstrated more treatment failures when the doxorubicin dose was decreased by 50%, although a retrospective analysis suggests that this effect may be limited to the human epidermal growth factor receptor 2 (HER2) overexpressing subset.[23,24] In other words, higher-dose CAF might only be beneficial in patients with HER2-overexpressing tumours, while dose reductions had no negative impact on the HER2 non-overexpressers. HER2 testing has been completed and will be reported for the Scandinavian trial in the future.

Rodenhuis et al.[25] reported preliminary data from the Dutch National randomised trial involving 885 patients having four or more positive axillary lymph nodes. These patients were randomised to receive FEC standard dosages five times or FEC four times, followed by a high-dose CTCb regimen. Preliminary analysis of the first 284 patients (who had the longest follow-up) demonstrated a relapse-free and overall survival advantage for the high-dose arm. However, when all 885 patients were included in the analysis, a statistical advantage and event-free survival were not seen. This study was recently updated,[26] with a median follow-up time of 57

months. At this time, a different subset of patients was found to benefit: patients with ten or more positive lymph nodes had improved relapse-free survival of 61% in the high-dose chemotherapy arm compared with 51% in conventional-dose group. In this study, there were two planned subgroup analyses: those of patients at intermediate risk defined as four to nine axillary lymph nodes positive for tumour; and high-risk patients with ten or more positive lymph nodes. Subgroup analysis was also performed on HER2 expression among a range of predictive factors. In patients with HER2-negative overexpressing tumours, the recurrence-free survival was significantly longer after high-dose chemotherapy than conventional therapy. There was a 34% reduction in the risk of recurrence, with a trend towards a benefit in survival. It is speculated that the improvement in recurrence-free survival in the high-risk group may be confined to HER2 overexpression-negative patients. However, it is important to note that the overall study fails to demonstrate a benefit.

Taking all the evidence together from the five published randomised trials in adjuvant setting testing high-dose chemotherapy, there is no evidence of an improvement in overall survival and there are mixed results, at best, in terms of improved event-free survival. Preliminary data from the Anglo-Celtic trial reported in 2002[27] lend further support to this assessment. In this trial 605 patients with a median of nine positive lymph nodes were randomly assigned to receive either high-dose chemotherapy (cyclophosphamide 6.0 g/m$^2$, thiotepa 800 mg/m$^2$) or doxorubicin 75 mg/m$^2$ for four cycles followed by CMF. The estimated event-free survival at 5 years for high-dose and conventional-dose chemotherapy is 51% and 54%, respectively. The estimated overall survival rates at 5 years are 63% and 62%, respectively. Similar findings were also reported by Tallman et al.,[28] where a conventional doxorubicin-containing regimen (CAF) was compared with the same standard chemotherapy followed by high-dose chemotherapy. With 6.1 years' median follow-up, there was no difference in the disease-free survival – 47% for standard-dose CAF versus 49% for CAF high-dose chemotherapy. For a summary of randomised clinical trials of high-dose chemotherapy in adjuvant setting in breast cancer, see table I.

## 2. RCTs of High-Dose Chemotherapy in the Metastatic Setting

Of the trials reported in metastatic disease (table II), none has demonstrated clear benefit in terms of overall survival. The French PEGASE-04 (French Study Group on High Dose Chemotherapy and Stem Cell Transplantation in Breast Cancer) trial[7] randomly assigned 61 patients following standard anthracycline-based chemotherapy to receive either two additional courses of standard chemotherapy or to receive high-dose chemotherapy – mitoxantrone 45 mg/m$^2$, cyclophosphamide 120 mg/m$^2$ and melphalan 140 mg/m$^2$. Median progression-free survival was prolonged in the high-dose arm compared with the standard-dose arm: 26.9 versus 15.7 months. The median survival was also improved: 36.1 versus 15.7 months. However, because of the small number of patients, these findings were not statistically significant.

The Philadelphia study[12] described 180 patients randomised to standard treatment versus a single high-dose treatment arm. In this study 553 patients with metastatic disease were initially treated with CAF or CMF (four or six cycles at physician discretion). Those who responded were then randomised to receive high-dose chemotherapy with the CTCb regimen plus transplantation of autologous hematopoietic stem cells or CMF in conventional doses. At 3 years, there was no difference in overall survival: 32% in the stem-cell transplant arm versus 36% for conventional therapy. Likewise, there was no significant difference between the two treatment arms for time to progression: 9.6 months in the high-dose chemotherapy group versus 9.1 months with conventional therapy. An update presented at the ASCO 2002 meeting[29] did not differ significantly. Critics of this study point out that patients randomised to the high-dose treatment arm received a smaller cumulative dose of chemotherapy than those treated on the standard arm with eight more cycles of standard chemotherapy, although that does not change the

**Table I.** Reported randomised controlled trials of high-dose chemotherapy (HDCT) for stage II/III breast cancer

| Trial | No. of patients | Treatment plan[a] | | Median follow-up | Outcome | Problem with study design |
|---|---|---|---|---|---|---|
| | | conventional CT | HDCT | | | |
| Rodenhuis et al.[8,21] | 97 | FEC[b] × 3 ↓ Surgery ↓ FEC[b] | FEC[b] × 3 ↓ Surgery ↓ FEC[b] ↓ CTCb[c] | 49mo | No difference in survival | Statistically underpowered Delay between induction and HDCT |
| Hortobagyi et al.[9] | 78 | FAC[d] × 8 | FAC × 8 ↓ CEP[e] × 2 | 6.5y | No RFS or OS advantage | Small study HDCT really intermediate dose |
| Peters et al.[10] | 783 | FAC[f] × 4 ↓ CPB[g] (intermediate dose) | FAC[f] × 4 ↓ CPB[h] (high dose) | 37mo | Inconclusive comparison between EFS and OS | High death rate due to toxicity Really a comparison between high- and intermediate dose |
| Bergh et al.[11,22] | 525 | FEC × 9 'tailored' | FEC × 3 ↓ CTCb[i] | 34.3mo | Tailored FEC associated with improved RFS and less grade 3–4 toxicities | Higher median-dose epirubicin in tailored group |
| Rodenhuis et al.[26] | 885 | FEC[j] × 5 | FEC[j] × 4 ↓ CTCb[c] | 57mo | Increased DFS in HDCT group; no difference in OS; possible benefit in HER2-negative tumours | If include all patients, no RFS advantage Trial needs to mature |
| Tallman et al.[28] | 511 | FAC[k] × 6 | FAC[k] × 6 ↓ CT[l] | 6.1y | No difference in DFS 47% conventional treatment), 49% HDCT | |
| Crown et al.[27] | 605 | A 75/m$^2$ × 4 ↓ CMF | A 75/m$^2$ × 4 ↓ CT[l] | 44.0 preliminary results | Estimated EFS: HDCT 51%; conventional treatment 54% OS at 5y: HDC 63%; conventional treatment 62% | Early study Another 15 events needed for 15% statistical analysis |

a Arrows represent schema of treatment.

b F 500 mg/m$^2$, E 120 mg/m$^2$, C 500 mg/m$^2$.

c C 6000 mg/m$^2$, T 480 mg/m$^2$, Cb 1600 mg/m$^2$.

d F 500 mg/m$^2$, A 50 mg/m$^2$, C 500 mg/m$^2$.

e C 1750 mg/m$^2$, E 400 mg/m$^2$, P 55 mg/m$^2$.

f F 1200 mg/m$^2$, A 60 mg/m$^2$, C 600 mg/m$^2$.

g C 900 mg/m$^2$, P 90 mg/m$^2$, B 90 mg/m$^2$.

h C 5625 mg/m$^2$, P 165 mg/m$^2$, B 600 mg/m$^2$.

i C 6000 mg/m$^2$, T 500 mg/m$^2$, Cb 800 mg/m$^2$.

j F 500 mg/m$^2$, E 90 mg/m$^2$, C 500 mg/m$^2$.

k F 500 mg/m$^2$, A 30 mg/m$^2$, C 100 mg/m$^2$.

l C 6000 mg/m$^2$, T 800 mg/m$^2$.

**A** = doxorubicin (adriamycin); **B** = carmustine (BCNU); **C** = cyclophosphamide; **Cb =** carboplatin; **CT** = chemotherapy; **DFS** = disease-free survival; **E** = epirubicin; **EFS** = event-free survival; **F** = fluorouracil; **HER2** = human epidermal growth factor receptor 2; **mo** = months; **OS** = overall survival; **P** = cisplatin; **RFS** = recurrence-free survival; **T** = thiotepa; **y** = years.

fact that a single cycle of high-dose chemotherapy was not better than prolonged standard therapy. Another issue was that the transplant on this trial could have been delayed up to 3 months after the end of conventional (induction) therapy.

An innovative, randomised, high-dose chemotherapy trial from Duke University (Durham, NC, USA) focused on the timing of haematopoietic stem cell transplant. Patients achieving a complete response were randomly assigned to immediate high-

dose chemotherapy versus observation with transplant at the time of subsequent progression. This large trial (423 patients) reported by Peters et al.[2,30] and Maden et al.[35] demonstrated a longer disease-free survival when the CPB high-dose regimen was given as consolidation immediately after achieving a complete response (125 patients) with conventional therapy (doxorubicin, fluorouracil, methotrexate two to four cycles). The disease-free survival was 24% at 5 years for patients who received high-dose treatment regimen and 8% for the closely observed group. In patients on the observation arm followed by a high-dose chemotherapy at relapse, the median overall survival was 3.6 years; those on the immediate high-dose chemotherapy arm had a median overall survival of 2.8 years. After 7 years, those having a delayed high-dose chemotherapy had an overall survival greater than 37%. If this benefit from late high-dose chemotherapy is substantiated, it would be of great importance. However, it is also important to recognise that this trial only addressed the timing, not the overall value, of the high-dose treatment.

Preliminary data from two other trials reported in abstract form[32,36] show no long-term advantage for high-dose chemotherapy. Schmid et al.[36] compared an upfront tandem, high-dose chemotherapy ap-

**Table II.** Reported randomised controlled trials of high-dose chemotherapy (HDCT) for metastatic breast cancer

| Trial | No. of patients | Treatment plan[a] | | Median follow-up | Outcome |
|---|---|---|---|---|---|
| | | conventional CT | HDCT | | |
| Lotz et al.[7] | 61 | Anthracycline-based CT × 4–6<br>↓<br>Anthracycline-based CT × 2 | Anthracycline-based CT × 4–6<br>↓<br>CMA[b] | | Median PFS: 15.7mo conventional CT vs 26.9mo HDCT<br>No statistical difference, although with a trend for HDCT group in median OS: 15.7mo conventional CT vs 36.1mo HDCT |
| Stadtmauer et al.[12,29] | 199 | Induction CT with CAF or CMF<br>↓<br>CMF | Induction CT with CAF or CMF<br>↓<br>CTCb[c] | 67.5mo | No difference in OS at 3y<br>25.8mo HDCT<br>26.1mo conventional CT<br>No difference in median time to progression<br>9.6mo HDCT; 9.1mo conventional CT[d] |
| Peters et al.[30,31] | 423 | AFM[e] × 2–4<br>↓<br>observation | AFM[e] × 2–4<br>Or<br>Relapse during observation<br>↓<br>CPB[f] | 108mo | Improved EFS for patients who achieved complete response with immediate HDCT<br>Delayed HDCT had better OS for patients who achieved complete response and 12% TRM |
| Biron et al.[32,33] | 180 | FEC[g] × 4<br>↓<br>No treatment | FEC[g] × 4<br>↓<br>CT[h] | 48mo | 3y OS: 30% conventional CT; 38% HDCT<br>Long-term advantage of HDCT not demonstrated |
| Schmid et al.[34] | 93 | AT[i] × 6–9 | CEM[j] × 2 | 14mo | OS: 27.7mo HDCT vs 20.8mo for conventional CT<br>PFS: 13.0mo HDCT vs 10.6mo for conventional CT ($p = 0.05$) |

a Arrows represent schema of treatment.

b Cyclophosphamide 120 mg/m$^2$; mitoxantrone 45 mg/m$^2$; melphalan 140 mg/m$^2$.

c Cyclophosphamide 1500 mg/m$^2$; carboplatin 200 mg/m$^2$; thiotepa 125 mg/m$^2$.

d Subgroup analysis showed a trend toward longer time to tumour progression for estrogen receptor protein + patients with CMF.

e Doxorubicin (adriamycin) 25 mg/m$^2$; fluorouracil 500 or 750 mg/m$^2$; methotrexate 250 mg/m$^2$.

f Cyclophosphamide 5625 mg/m$^2$; cisplatin 165 mg/m$^2$; carmustine (BCNU) 600 mg/m$^2$.

g Fluorouracil 500 mg/m$^2$; cyclophosphamide 500 mg/m$^2$; epirubicin 100 mg/m$^2$.

h Thiotepa 800 mg/m$^2$; cyclophosphamide 6000 mg/m$^2$.

i Doxorubicin 60 mg/m$^2$; paclitaxel 200 mg/m$^2$.

j Cyclophosphamide 4400 mg/m$^2$; etoposide 2500 mg/m$^2$; mitoxantrone 45 mg/m$^2$.

**CAF** = cyclophosphamide, doxorubicin, fluorouracil; **CMF** = cyclophosphamide, methotrexate, fluorouracil; **CT** = chemotherapy; **EFS** = event-free survival; **mo** = months; **OS** = overall survival; **PFS** = progression-free survival; **TRM** = treatment-related mortality; **y** = years.

proach (cyclophosphamide 4.4 g/m$^2$, mitoxantrone 45 mg/m$^2$ and etoposide 2.5g/m$^2$) to standard doxorubicin 60 mg/m$^2$ and paclitaxel 200 mg/m$^2$.[36] Ninety-two patients were randomly assigned in this trial. At a median follow-up of 14 months, the overall survival was similar: 28.4 months (high-dose chemotherapy) versus 25.3 months in the standard doxorubicin and paclitaxel (AT) arm. The progression-free survival was 14.3 months with high-dose chemotherapy and 10.3 months with conventional therapy. With a relatively short median follow-up, the investigators concluded that high-dose chemotherapy was associated with a significantly longer progression-free survival, although no differences were noted in the overall survival. When these data were updated with longer follow-up,[34] the overall survival was 27.7 months for the high-dose treatment group and 20.8 months for the conventional treatment group. The complete response rate was similar for both groups: 12.5% and 11.1% in the high-dose and conventional treatment groups, respectively, and the overall response rates were likewise similar between the groups: 64.6% in the high-dose treatment group, 62.2% in the conventional treatment group. Schmid et al.[34] noted, in contrast to the earlier analysis,[36] that there was no difference in response rate, time to progression and overall survival. Likewise, Biron et al.[32] presented the results of 180 patients randomly assigned to high-dose treatment on the French PEGASE-03 protocol trial. This was a prospective, multicentre trial where patients were treated with thiotepa 800 mg/m$^2$ and cyclophosphamide 6000 mg/m$^2$ versus observation after four cycles of FEC 100. While the 3-year overall survival was 30% in the observation arm and 38% in the high-dose chemotherapy arm; a long-term advantage for high-dose chemotherapy was not demonstrated.

A nonrandomised comparison between high-dose and standard-dose chemotherapy in metastatic breast cancer was recently reported by the CALGB.[37] In this analysis, the results of four CALGB trials employing anthracycline-based, conventional-dose chemotherapy were compared with those of patients treated with high-dose chemotherapy from the ABMTR. The analysis was based on 1509 patients treated in CALGB trials and 1185 women treated through the ABMTR, but restricted to 635 treated with conventional-dose chemotherapy and 441 with high-dose chemotherapy. The investigators concluded that women treated with high-dose chemotherapy may have a slightly higher probability of long-term survival: 3- and 5-year probabilities were 37% and 22%, respectively in the high-dose treatment arm versus 27% and 23%, respectively in the conventional-dose treatment arm. The probability of short-term survival appears similar for both groups. In this analysis, all patients were less than 65 years of age. Confounding this analysis was the observation that those in the high-dose treatment arm had a slightly better performance status and the overlaying issue that these were not random assignment trials. While this data set could support the hypothesis that high-dose chemotherapy and trials designed to test it might be superior, it could not establish superiority for this approach.

Recently, Crown et al.[38] reported results from a randomised trial of tandem, transparent versus standard doxorubicin, docetaxel four cycles followed by cyclophosphamide, methotrexate, cisplatin (CMP) four cycles in metastatic breast cancer.[38] Although the study was prematurely stopped as a result of poor accrual, results of 110 patients out of a planned 264 are available. With a primary endpoint of event-free survival at 3 and 5 years in favour of the high-dose treatment arm (16% vs 9% in high-dose and standard therapy, respectively, at 3 years and 14% vs 7%, respectively at 5 years [median follow-up of 47 months]), the investigators conclude that high-dose chemotherapy is still a valid investigational strategy.

## 3. Conclusion

To date, a clinically relevant benefit for high-dose chemotherapy in the treatment of breast cancer has not been demonstrated, and this approach cannot be recommended outside of well designed prospective studies.

In patients with advanced breast cancer, the available data suggest that a small proportion of

patients (<20%) may achieve long-term, disease-free survival with high-dose chemotherapy,[17,39] but enjoy no improvement in overall survival. Whether this represents a better outcome than would be obtained with less toxic standard therapy is still unknown. In the adjuvant setting, there is even less evidence of benefit from high-dose chemotherapy.

On the other hand, the decade-long experimentation by medical oncologists with high-dose chemotherapy is not without benefit. While the technological advances developed in breast cancer patients regarding stem-cell harvest, growth-factor production and supportive care (with respect to antibacterial and blood product use) may ultimately not benefit breast cancer patients, they undoubtedly have improved the treatment of patients with other chemotherapy-sensitive tumours.[2]

In the meantime, new active drugs, such as taxanes, have emerged as important with confirmed benefits in both disease-free and overall survival, particularly for early-stage disease.[40] With these and other conventional agents another approach to improving treatment may be to change the interval of drug administration as has been reported recently by Citron et al.[40] In this trial (CALGB 9741 – an Intergroup trial), patients received sequential or concurrent doxorubicin and cyclophosphamide along with single-agent paclitaxel. All patients were also randomised to treatment using a more dose-dense 2-week interval supported with G-CSF (filgrastim) or in conventional schedule (3-week intervals). There were 1973 patients accrued between September 1997 and March 1999. Forty-one percent of the patients had four or more positive lymph nodes. At 36 months' median follow-up, the dose-dense approach was associated with a 26% proportional reduction in relapse. The 4-year disease-free survival was 82% for the dose-dense regimen compared with 75% for the every-3-week schedule, and the dose-dense treatment arm was associated with a 31% proportional reduction in mortality. The overall survival was 92% in the dose-dense and 90% in the every-3-week regimen. The toxicity profile was similar in both arms with the exception of 3–5% of patients in the 3-week schedule who were hospitalised for febrile neutropenia in contrast to 2% treated in the dose-dense fashion. These data suggest that dose and schedule may have an impact on outcome, but that the simple expedient of escalating the size of single doses may be insufficient.

## Acknowledgements

The authors wish to thank Carol Pearce for her assistance in editing, and Emily Charette for her assistance in the preparation of this manuscript.

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

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