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Commentary

High-dose chemotherapy in breast cancer—interpretation of the randomized trials

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High-dose chemotherapy was widely viewed as an effective treatment modality in breast cancer until the preliminary results of randomized trials proved disappointing. When it transpired that the author of the two unequivocally positive studies had fabricated data, many decided that high-dose chemotherapy in breast cancer was no longer worth studying. In fact, however, the reported results from randomized studies are consistent with a modest progression-free survival advantage of high-dose chemotherapy over conventional dose. Several more years of data maturation and the results of additional randomized trials must be awaited. **[© 2001 Lippincott Williams & Wilkins.]**

Key words: Adjuvant chemotherapy, bone marrow transplantation, breast cancer, high-dose chemotherapy, peripheral blood progenitor cell transplantation.

Introduction

In May 1999, the first large-scale randomized studies of high-dose chemotherapy were presented at the Annual Meeting of the American Society of Clinical Oncology. These reports caused a precipitous shift in opinion among both patients and doctors: while high-dose chemotherapy had been uncritically accepted as an important component of potentially curative treatment, now the available data were interpreted as essentially negative. When it was shown that the only positive report (that of Bezwoda from Witwatersrand University in South Africa) was in fact based on scientific fraud,[1] the final verdict appeared to be in: many believed this to be the end of high-dose therapy in breast cancer.

In reality, however, most of the evidence from randomized studies is consistent with a modest, but potentially important, beneficial effect of high-dose therapy. In addition, when armed with some basic knowledge of breast cancer treatment, pharmacology and tumor biology, it is easy to see that the so-called negative trials all suffered from important design flaws. They lacked statistical power, and had significant delays between the conventional part and the high-dose part of the chemotherapy or—paradoxically—administered inappropriately low-dose chemotherapy in their 'high-dose' arms (Table 1).

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Randomized studies in the adjuvant treatment of breast cancer

The first randomized study published was a single-institution study of the Netherlands Cancer Institute.[2] Eighty-one patients with breast cancer and extensive axillary node metastases who had received up-front chemotherapy and surgery were randomized to either receive additional conventional-dose chemotherapy or to undergo high-dose chemotherapy with peripheral blood progenitor cell transplantation. This study did not show any advantage for the high-dose arm, but it was powered only to detect a difference in survival exceeding 30%, and there was a long delay between conventional induction chemotherapy and high-dose therapy. Such a delay could obviously allow regrowth of micrometastatic tumor cells, leading to diminished efficacy of the induction therapy.

A second small single-institution study from the MD Anderson Cancer Center was reported in 2000.[3] A total of 78 patients with high-risk breast cancer who had received eight cycles of adjuvant chemotherapy were randomized to undergo either two courses of cisplatin, cyclophosphamide and etoposide or no further chemotherapy. This study did not show a (relapse-free) survival difference as well. Its statistical power to detect a difference was, however, very small

Table 1.

Trial	Outcome	Problems with study design
Stage II/III breast cancer		
Rodenhuis *et al.*[2]	negative	small study; delay between conventional and high-dose therapy
Hortobagyi *et al.*[3]	negative	small study; intermediate rather than high chemotherapy dose
Bezwoda *et al.*[12]		scientific fraud
Scandinavian group[13]	'conventional' therapy better	undertreatment in 'high-dose arm'; very high-dose intensity and high cumulative dose in 'conservative' arm
CALGB/Intergroup study[4]	less relapses in high-dose arm	preliminary data
Dutch study[7]	less relapses in high-dose arm	preliminary data
Advanced breast cancer		
Bezwoda[8]	positive	scientific fraud?
PEGASE study[9]	positive?	small study
Philadelphia study[10]	negative	delay between conventional and high-dose chemotherapy, CTCb regimen
Duke studies[11,12]	event-free survival advantage for high dose, delayed high dose better than immediate high dose	comparison not high versus conventional dose

and the 'high-dose' chemotherapy did not require a transplant.

At the 1999 ASCO meeting, the preliminary results of a large American Intergroup study were reported by Peters *et al.*[4] Seven hundred and eighty-three patients were randomized to receive four courses of conventional-dose CAF chemotherapy, which was either followed by high-dose cyclophosphamide, cisplatin and BCNU (CPB) or by an intermediate dose of CPB (that did not require a transplant). At this early analysis, there were no differences in event-free or overall survival, but there were significantly less relapses in the high-dose group (19.8 versus 27.5%). This advantage was, unfortunately, set off by a high toxic death rate of 7.4%.

A further study reported at the 1999 ASCO meeting was the Scandinavian study, which had randomized 525 patients to either nine courses of 'individually tailored' chemotherapy with fluorouracil, epirubicin and cyclophosphamide (FEC) plus granulocyte colony stimulating factor or three courses of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin (CTCb). The CTCb arm was labeled the 'high-dose arm', although the dose of chemotherapy in the individually tailored FEC arm was much higher. This study[5] actually shows an event-free survival advantage for the individually tailored FEC arm. This is not surprising, since the three FEC courses in the 'high-dose arm' contained a cumulative dose of only 180 mg/m^2 of epirubicin. This clearly represents under-treatment and decreasing the anthracycline dose by 50% has previously been shown to result in more treatment failures.[6]

The largest randomized study of high-dose chemotherapy in the adjuvant treatment of breast cancer was reported in preliminary form at the ASCO meeting in May 2000.[7] This Dutch national study randomized 885 patients with four or more positive axillary lymph nodes to receive either four courses of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin (CTC) or five standard-dose courses of FEC. An analysis of the first 284 patients in this trial showed a significant relapse-free and overall survival advantage for the patients receiving high-dose therapy. When all 885 patients were analyzed, however, the event-free survival advantage was not statistically significant. This analysis, however, requires at least two or more years of maturation.

In summary, both large randomized multicenter studies that test the concept of high-dose chemotherapy with peripheral blood progenitor cell transplantation have yielded preliminary evidence that high-dose therapy may have a (modest) event-free survival advantage.

High-dose chemotherapy in advanced breast cancer

The results of four randomized studies of high-dose chemotherapy in advanced breast cancer have been reported, either as a full publication in a peer-reviewed journal or as a meeting abstract.

The first is a study by Bezwoda,[8] which showed a survival advantage for high-dose therapy. This evidence should, however, not be taken into account because of Bezwoda's scientific misconduct.

A second study was reported at the 1999 ASCO meeting by the French PEGASE group.[9] This small multicenter study randomized 61 patients who had responded to standard-dose chemotherapy. Two to four additional cycles of conventional chemotherapy were compared with a course of high-dose chemotherapy with mitoxantrone, cyclophosphamide and melphalan. The median time to progression was 35 months in the high-dose group versus 20 months in the standard-dose group and the median survival was 43 months in the high-dose group versus 20 months in the standard-dose group. Possibly as a results of the small number of patients, however, these differences were not statistically significant.

The most widely publicized randomized study in advanced breast cancer is that of Stadtmauer *et al.*, frequently called the 'Philadelphia study'.[10] This small study (166 randomized patients) failed to show a difference in disease-free survival between patients randomized to the standard-dose arm and those randomized to the high-dose arm. This results strongly argues against the previously common practice of administering CTCb chemotherapy routinely several months after a response to conventional-dose chemotherapy. The study had a number of important limitations, however:

- Patients in the 'conventional chemotherapy' group received a substantially higher cumulative dose of chemotherapy than those randomized to the 'high-dose' group: eight additional courses of CMF chemotherapy versus a single course of CTCb.
- Patients were randomized at a maximum of 8 weeks after the last dose of conventional chemotherapy. Following this a bone marrow harvest and/or stem cell mobilization and harvest had to take place, and patients were than scheduled for high-dose chemotherapy. As a result there could be up to 3 months delay between the last conventional chemotherapy and the actual start of high-dose therapy. As in other studies, this could have allowed tumor regrowth during the chemotherapy-free interval.

Finally, randomized data from studies at Duke University have been reported.[11,12] These studies indicated that patients with advanced breast cancer who obtain a complete remission with conventional-dose chemotherapy have a significantly longer disease-free survival when consolidation treatment with high-dose chemotherapy (CPB) is administered. Overall survival, however, may increase by administering high-dose chemotherapy late rather than early after obtaining the objective response. These data are difficult to interpret, since the comparison is not high-dose chemotherapy versus conventional dose, but immediate versus delayed high-dose therapy.

Conclusion

At this point in time the efficacy of high-dose chemotherapy in breast cancer is unproven. In the metastatic setting, there are simply no large well-designed trials. Such trials are ongoing, but have suffered badly from the recent negative publicity. Large trials of high-dose therapy in the adjuvant setting are available, but these have either not been reported at all or are too early for firm conclusions. Both large studies that compare high-dose chemotherapy with conventional-dose chemotherapy suggest a lower proportion of relapses in the high-dose arms. It is clearly inappropriate to interpret this lack of mature and statistically significant results as the absence of benefit of high-dose therapy. It is interesting to compare the current situation with that for doxorubicin in adjuvant therapy in previous years. Only in the year 2000, the fifth overview of the Early Breast Cancer Trialists' Collaborative Group presented evidence that the use of anthracyclines may significantly improve adjuvant therapy in breast cancer over CMF-like regimens. Some 14 000 randomized patients and over 2 decades of clinical research were needed to establish this. Viewed against this background, proponents of high-dose therapy in breast cancer should be granted a few more years to prove their case.

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