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# High dose therapy in metastatic breast cancer

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## Keywords

High dose therapy, metastatic breast cancer

# Introduction

The majority of patients with metastatic breast cancer respond to front-line conventional-dose chemotherapy. Unfortunately, nearly all still die within 10 years of diagnosis. In the late 1980's a number of reports suggested that results in patients with chemotherapy-responsive disease could be significantly improved by utilising high-dose chemotherapy supported by autologous haematopoietic stem-cell transplantation. Not only were high overall rates of response reported (in some studies up to 100%), but up to 20% of patients had 5-year progression-free survivals. These results looked particularly impressive when comparisons were made with the results from earlier studies using conventional treatment approaches, and conceivably could improve further with advances in supportive care decreasing the toxicity of high-dose therapy. The widespread publicity associated with these early noncomparative studies led to a rapid acceptance of high-dose strategies as an appropriate therapeutic approach to the treatment of metastatic breast cancer, despite any randomised phase III data.

# Aims

To compare high-dose chemotherapy plus haematopoietic stem-cell rescue with a prolonged course of monthly conventional-dose chemotherapy in patients with responsive metastatic breast cancer, in terms of overall survival, the time to progression, and toxicity.

# Comments

This study found no clinical benefit for this particular high-dose therapy regimen in women with responsive metastatic breast cancer, and further analysis failed to identify any patient subgroup for whom the more aggressive therapy was beneficial. This result appears to contradict the promising results and conclusions reported by earlier phase II studies (see Additional Information), emphasising the

importance of properly conducted randomised phase III trials in determining effectiveness of new treatment strategies. The results support the contention of some authors that the supposedly superior results seen in phase II studies of high-dose therapy were largely as a result of selection bias due to stringent entry criteria. There are a number of weaknesses in the study, particularly the fact that the number of patients randomised while in complete remission was relatively small, and so it is possible that a small survival benefit for high-dose therapy in this group of women was not detected. In addition, the follow-up has been reasonably short. It is also unclear if a single cycle after induction therapy is the most effective high-dose strategy. Other approaches, including multiple consecutive transplantations and different chemotherapy regimens, are currently being evaluated. This report is the latest of a number of recent trials addressing high-dose therapy in breast cancer. Apart from one now totally discredited trial, these have all failed to demonstrate a significant benefit for high-dose therapy over conventional approaches, and should lead the supporters of high-dose therapy to question the ethics of applying this form of treatment outside of appropriately designed clinical trials.

# Methods

Women with previously untreated metastatic or locally recurrent breast cancer responding to between four and six cycles of standard combination chemotherapy (either CMF [cyclophosphamide, methotrexate, and fluorouracil] or an anthracycline-based regimen) were entered into the study. They were then randomised to receive either conventional dose CMF or a single cycle of high dose carboplatin, thiotepa, and cyclophosphamide followed by an autologous haematopoietic stem cell transplant.

# Results

Patients ($n$ = 553) were treated with conventional induction chemotherapy and 310 responded (58 complete responses [CR] and 252 partial responses). From the 310 responders, 199 went onto the next phase of the study, with 110 assigned to high-dose and 89 receiving conventional-dose chemotherapy. The skewed assignment was due to an attempt to balance the randomisation for numerous stratification factors. Of these, 15 patients were found to be ineligible and were not included in the primary analysis and a further 20 then refused their treatment assignment. Nevertheless, there were no significant differences between the two treatment groups. With a median follow-up of 37 months no significant difference was found in median survival (26 months conventional vs 24 months high-dose) or in 3-year overall survival (38% conventional vs 32% high-dose). Patients in both groups consistently had a higher rate of survival if they were in the CR group at the time of randomisation. There were also no significant differences in survival within the other subgroups analysed. Median time to disease progression (9.0 months conventional vs 9.6 months high-dose, $P$ = 0.31) was similar. With regards to toxicity, patients in the high-dose arm had a higher rate of severe haematological toxicity as well as infection, diarrhoea, and vomiting. No lethal adverse effects were reported in the conventional-chemotherapy group.

# Discussion

In women with metastatic breast cancer achieving a complete or partial remission with conventional-dose chemotherapy, high-dose chemotherapy plus autologous stem-cell transplantation does not appear to produce better results than maintenance chemotherapy at conventional doses. Although follow-up is relatively short, the number of patients who survived for three years without signs of disease progression was so low that it is unlikely that the results will change significantly with continued follow-up.

# Additional information

Previous phase II studies that appeared to show benefits of high-dose chemotherapy:

Peters WP *et al* High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol* 1988, **6**:1368-76.[Abstract]

Williams SF *et al* High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *J Clin Oncol* 1989, **7**:1824-30.[Abstract]

Kennedy MJ *et al* High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intense induction as initial therapy for metastatic breast cancer. *J Natl Cancer Inst* 1991, **83**:920-6.[Abstract]

Antman K *et al* A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol* 1992, **10**:102-10.[Abstract]

Williams SF *et al* High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report. *J Clin Oncol* 1992, **10**:1743-7.[Abstract]

# References

1. Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN, Brodsky I, Martino S, Lazarus HM, Erban JK, Sickles C, Glick JH, Luger SM, Klumpp TR, Litzow MR, Litzow MR : Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. New Engl J Med. 2000, 342: 223-229.