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High-dose chemotherapy in high-risk breast cancer

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Keywords

Breast cancer, chemotherapy, high-dose, high-risk

Introduction

The addition of systemic therapy to loco-regional therapy has resulted in a highly significant increase in the survival of patients with high-risk primary breast cancer. Nevertheless, many of these patients still relapse and die, presumably due to the presence of persistent micrometastatic disease. On the basis of both *in vitro* evidence that many cytotoxic agents have steep dose-response curves, and clinical trial data indicating a dose-response within the standard dose range, many investigators proposed the use of very high dose chemotherapy regimens in an effort to eradicate these persistent micrometastases with the aim of improved survival rates. The use of blood stem cell autografts facilitated this process and markedly improved the safety of these regimens. Uncontrolled trials of high dose chemotherapy in metastatic disease demonstrated high response rates and early phase II adjuvant trials in high-risk patients appeared to demonstrate superior relapse-free survival rates compared to results of standard therapy.

Aims

To compare standard dose chemotherapy to the same therapy followed by high dose chemotherapy in patients with high risk breast cancer.

Comments

Although this study was small, it was powered to detect a 30% benefit in 3-year relapse-free survival for the high-dose therapy arm - this failed to occur. The possibility of a smaller benefit remains, and this will hopefully be determined by the results of larger US and European studies. Nevertheless, this area of research/treatment remains controversial, with the supporters of high-dose therapy sticking to their beliefs that this approach is of value in the treatment of breast cancer. Despite the recent publication of a number of randomised studies failing to support high-dose therapy, questions remain regarding the most

appropriate regimen, the optimal number of high-dose cycles, the best timing of high-dose therapy, and which group of patients to target. This study provides further support for the contention that high-dose chemotherapy in breast cancer remains an unproven therapy that should only be given as part of ongoing clinical trials.

Methods

Patients were eligible for the study if they had either operable stage II or stage III primary breast cancer with greater than nine involved lymph nodes, or if following four cycles of induction chemotherapy for stage III or locally advanced breast cancer they had four or more persistent pathologically positive nodes. Patients received eight cycles of standard dose FAC chemotherapy (5-fluorouracil, adriamycin and cyclophosphamide), and then no further cytotoxic therapy or two cycles of high dose CEP (cisplatin, etoposide and cyclophosphamide) supported with autologous blood stem cell or bone marrow transplantation. All patients had postchemotherapy radiation and postmenopausal oestrogen-receptor-positive patients also received tamoxifen for 5 years.

Results

Over 8 years, 78 patients were accrued (48 after initial surgery and 30 after induction chemotherapy), with 39 randomised into each arm. The patient characteristics were similar between the two groups. Of the 39 patients randomised to receive standard FAC alone, 36 completed treatment, with four developing recurrence during treatment; three patients elected to go on to receive high-dose therapy at other institutions. Of the 39 patients randomised to receive high dose chemotherapy, 31 received treatment as scheduled. Of these, four developed metastases during the FAC component - the same number as in the standard arm, while the other 27 went on to have high-dose therapy. A further two patients had other high-dose schedules. Median follow up of live patients was 6.5 years in each group. The estimated 3-year relapse-free survival on an intention-to-treat analysis was 62% in the standard arm and 48% in the high-dose arm ($P = 0.35$), whilst on an actual-treatment-delivered analysis, the 3-year survival figures were 59% and 52% ($P = 0.7$), respectively. The calculated overall 3-year survival rates by intention-to-treat analysis were 77% and 58% respectively ($P = 0.23$), whilst for actual-treatment-delivered analysis the figures were 73% *versus* 61% ($P = 0.54$). There was no evidence that the results differed between the patients undergoing immediate surgery and those who first had induction chemotherapy. Standard dose FAC was tolerated well and the observed toxicities were as expected and similar between the two arms. With high-dose therapy, there was one septic death, one case of acute myeloid leukemia, three cases of persistent peripheral neuropathy and two patients with grade 3 cardiac toxicity.

Discussion

The patients did better than expected in both arms, possibly due to the beneficial effects of patient selection. Nevertheless, there was no evidence of clinical benefit in terms of either disease-free or overall survival for patients receiving two cycles of high-dose chemotherapy following standard dose adjuvant therapy.

References

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