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Commentary

Whither high-dose chemotherapy in breast cancer?

Astrid Mayer and Helena Earl

Department of Oncology, Addenbrooke's Hospital, Cambridge, UK

Correspondence: Helena Earl, Department of Oncology, Box 193, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK. Tel: +44 01223 336 800; fax: +44 01223 412 213; e-mail: hme22@cam.ac.uk

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Abstract

Four trials of high-dose chemotherapy with stem cell support in breast cancer in the adjuvant and metastatic settings have shown no long-term disease-free or overall survival gain. This relative failure of a single high-dose therapy we believe opens up the development of a dose-dense approach with block scheduling as the most promising way forward. This intensive chemotherapy can be more easily combined with the newer biological therapies and our prediction is that this will prove to be the most effective treatment in the future for women with poor risk breast cancer.

Keywords: breast cancer, high-dose chemotherapy

Introduction

Our intended pun implies that we have reached a crossroads in high-dose chemotherapy for breast cancer. Is high-dose chemotherapy going anywhere, or should we allow it to wither on the vine? The conclusion of this commentary is that, in its present form, high-dose treatment has not been found to be superior to conventional-dose treatment in either the metastatic or adjuvant setting. However, we should be careful not to 'throw the baby out with the bath water'. Rather, we should look seriously at intensifying chemotherapy with more active drugs, given in different schedules. Our judgement is that using conventional cytotoxic chemotherapy, the approach pioneered by the Memorial Sloan-Kettering Hospital, New York, USA, with 'dose-dense' chemotherapy given in a 'block schedule', is likely to produce the best results [1]. However, there is also now much to be gained from looking at biological agents in combination with conventional chemotherapy, particularly with the recent encouraging results with the use of trastuzumab (Herceptin, Genentech, San Francisco, CA, USA) [2].

High-dose chemotherapy in breast cancer has been a controversial issue for some time. Several phase 2 trials showed promising results in patients with chemotherapy-responsive metastatic disease, when the data were compared with the outcome in historical control individuals [3,4]. However, most recently published randomized trials demonstrate a lack of effectiveness in both the adjuvant and metastatic settings [5–8]. The trials of Bezwoda and coworkers from South Africa [9–12] remained the only important positive evidence for high-dose chemotherapy, until the publication of the onsite review of the Bezwoda studies [13] and the investigator's admission of serious scientific misconduct. Although international commentators [14,15] have suggested that further trials of high-dose chemotherapy should be carried out, our view is that such studies will have to be innovative enough to persuade oncological clinical investigators worldwide that this approach is worth investigating further.

The concept of dose intensity is based on the hypothesis that a single or tandem exposure to very high doses of chemotherapy will eliminate any remaining tumour cells, and thereby result in a cure. High-dose treatment is based on escalating the dose of chemotherapeutic agents, in particular alkylating agents, which will result in severe bone marrow depression. The technique of autologous bone

marrow transplantation and more recently the use of peripheral blood stem cells to restore marrow function have made this approach possible.

There is considerable *in vivo* evidence that dose intensification can improve responses in breast cancer. One of the first studies was performed by Bonadonna *et al* [16]. Those investigators analyzed two of their clinical trials retrospectively, and reported that patients who received a higher percentage of the intended dose of chemotherapy had a significantly longer disease-free survival. Review of patients in adjuvant and palliative breast cancer trials [17,18] suggested a linear dose–response relationship for patients receiving conventional doses of chemotherapy. This was particularly steep once the threshold intensity had been surpassed. A prospective study by the Cancer and Leukemia Group B [19] confirmed that both premenopausal and postmenopausal women receiving high or moderate doses of cyclophosphamide, doxorubicin and fluorouracil had significantly better disease-free and overall survival than those receiving low doses. A meta-analysis of 14 studies with higher doses without bone marrow support in metastatic breast cancer showed a survival advantage, although this was modest [20].

In the 1980s, high-dose treatment with bone marrow support was introduced into breast cancer treatment after it had proven successful in more chemosensitive diseases such as leukaemia and lymphoma. Disappointingly, four studies [5–8], including more than 1400 patients receiving adjuvant treatment, failed to prove an advantage in the adjuvant setting. Similarly, there was no survival benefit in patients with metastatic disease, although a higher response rate was reported [21,22].

A variety of reasons potentially account for this. One hypothesis is that the dose–response curve usually has a sigmoid shape with a threshold, a lag phase, a linear phase and a plateau phase [23]. The dose–response curve is steep in the linear phase. Reduction of dose intensity in the linear phase results in a marked decrease in cure rates before a significant reduction in the complete remission rate. On average, a dose reduction of 20% leads to a loss of 50% in the cure rate. Increasing the dose intensity can therefore be a useful way to increase the effect of certain drugs. This potentially explains the benefit of more dose intense, conventional regimens, as found by Bonadonna *et al* [16] and Wood *et al* [19]. In contrast to other malignancies such as lymphoma, the dose–response curve for breast cancer seems to be shifted to the left, and escalating doses to the levels used for the high-dose treatment may reach the plateau phase.

Intrinsic resistance to the available chemotherapeutic drugs and the development of resistant clones during chemotherapy are also likely to be partly responsible for the failure of high-dose chemotherapy to impact on the survival of breast cancer patients. Some years ago Goldie and Coldman developed a mathematical model that predicted that mutations causing drug resistance occur in tumours of 10^3–10^6 tumour cells [24], which is much lower than the clinically detectable level (ie a tumour at detectable level would be almost certain to have at least one drug-resistant clone, if not more).

Another reason for the failure of high-dose treatment in breast cancer is the choice of drugs available for dose escalation. The drug combinations used include mostly alkylating agents and platinum. Unfortunately, some of the most effective drugs in breast cancer, namely anthracyclines and taxanes, are not suitable for dose escalation to the same extent because of the cardiotoxicity of anthracyclines and neurotoxicity of taxanes.

Conclusions

Perhaps with the resounding failure of conventional high-dose chemotherapy approaches in breast cancer, we should turn our attention to the 'dose-dense' approach with the block scheduling suggested by the mathematical models of Day [23], and developed clinically by Norton and Day [1]. Our expectation of high-dose treatment with bone marrow support has thus far not been fulfilled either in the adjuvant or in the metastatic setting. A dose-intense conventional approach remains the 'gold standard'. Although there is a variety of treatment options available, further research is needed to explore different ways to find improved treatment strategies. The recent introduction of Herceptin, a cerbB2 antibody, into the clinic, which has been shown to improve survival in patients with metastatic disease, is one step in that direction.

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