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Editorial Comment

Is high-dose chemotherapy dead?

Sjoerd Rodenhuis *

Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, Amsterdam, Netherlands

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The story of high-dose chemotherapy in breast cancer is a remarkable one and it contains a number of valuable lessons for all of us. Many oncologists believe that this story has come to an end and that the further study of this treatment modality is no longer worthwhile. However, such a belief could be just as premature and thoughtless as the uncritical use of high-dose chemotherapy that was so common 10 years ago.

Small phase I and II studies in the 1980s had shown that high-dose chemotherapy in advanced breast cancer was associated with unusually high complete response rates, and that long-term disease-free survival was observed in a proportion of patients [1]. Similar findings were reported from the American and European bone marrow transplant registries. Approximately 20% of patients with stage IV disease appeared to be free of disease five years after the transplant and this finding raised hope that breast cancer could eventually take its place among the malignancies that are curable by chemotherapy. In 1993, a highly provocative study was published by Peters and colleagues, which showed that high-dose chemotherapy administered in the adjuvant setting to patients with high-risk primary breast cancer could achieve a 5-year disease-free survival of 70%. This appeared to be dramatically superior to conventional chemotherapy in historical controls [2]. Supported by a strong rationale derived from laboratory studies [3], but in the absence of data from randomised trials, high-dose chemotherapy was adopted as a potentially curative treatment option. Particularly in the United States, randomised studies with a conventional control arm were difficult to conduct since patients and doctors alike believed in the concept. As a result, the number and size of clinical studies initiated to prove or disprove its value was insufficient. In 2000, it became clear that the only controlled studies with evidence of a survival benefit for high-dose therapy were in fact fraudulent and that the patients described in them did not even exist [4]. A shockwave went through the Medical Oncology community. When a small number of randomised studies by reputable groups did not show overall survival benefits, the scene was set for the demise of high-dose chemotherapy in breast cancer.

It is against this background, that the paper of the PEGASE-4 (French High-Dose Chemotherapy in Breast Cancer Group) study by Lotz *et al.* [5] in this issue of the journal must be interpreted. This study shows a benefit for high-dose chemotherapy with cyclophosphamide, melfalan and mitozantrone in patients with stage IV disease following conventional-dose induction chemotherapy. Clearly, with only 61 randomised patients, the study is very small and a difference in outcome could be attributed to some unapparent but existing difference in the biology of the cancers between the two groups. The study must also be compared with 5 other studies comprising some 800 patients studying the value of high-dose therapy in advanced breast cancer (Table 1). Like the PEGASE-4 study, all except the 'Philadelphia study' [6] show a significantly prolonged relapse-free survival for the high-dose chemotherapy arm. However, none except perhaps the IBDIS-1 study [7] shows a significant improvement in overall survival. Interestingly, the PEGASE-4 study has a few long-term disease-free survivors (19%) in the high-dose arm, but none after conventional-dose chemotherapy only.

One hypothesis that could explain most of the findings is, that a subgroup of breast tumours exist that are exquisitely sensitive to high-doses of alkylating agents. Patients with this type of tumour may benefit

* Tel.: +31 205122870; fax: +31 205122572.
E-mail address: s.rodenhuis@nki.nl

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Table 1
Randomised studies of high-dose chemotherapy in stage IV breast cancer

Study [Ref.]	*N*	Conventional arm	High-dose arm	RFS	OS
Philadelphia [6]	199	Up to 24 × CMF	1 × High-dose	Same	Same
PEGASE 03 [8]	180	No further treatment	1 × High-dose	Better	Same
PEGASE 04 [5]	61	4–6 × Conventional, then 'maintenance'	4–6 × Conventional, then 1 × High-dose	Better	Better: $P<0.03$
IBDIS-1 [7]	110	4 × AT + 4 × CMF	4 × AT then 2 × High-dose	Better	Better?
NCIC [9]	219	2–4 × Conventional	1–2 × Conventional, then 1 × High-dose	Better	Same
German [10]	92	6–9 × Doxorubicin and paclitaxel	2 × HD	Better	Same

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; AT, doxorubicin and paclitaxel; RFS, relapse-free survival; OS, overall survival; NCIC, National Cancer Institute of Canada; IBDIS, International Randomised Breast Cancer Dose Intensity Study.

significantly from high-dose therapy and some with disseminated disease may even achieve long-term survival. If the percentage of tumours that has this property is around 15–20%, than this could explain the small groups of long-term disease-free survivors that are observed in many studies. Of course, long-term survivors after conventional-dose chemotherapy may also occur [11]. These could, for instance, represent patients with tumours that are extremely sensitive to anthracycline-based regimens. Breast cancer is, both clinically and biologically, a highly variable disease and the notion that resistance to one drug and sensitivity to another one may be present simultaneously in a single tumour is borne out on a daily basis in the clinic.

Thus, it would be important to identify tumours that are sensitive to high-dose alkylating agents and may even be eradicated by them. Retrospective studies [12,13] have shown that only younger patients (e.g., those below 50–55 years of age) with excellent performance status (World Health Organisation (WHO) 0 or 1) do well, and only when their tumour load is limited (1 or 2 sites of disease). Tumours that have relapsed after recent adjuvant chemotherapy do worse and patients with tumours that have been shown to be resistant against conventional-dose chemotherapy will certainly not benefit. High-dose therapy appears to be effective in stage IV patients with no evidence of disease (patients with stage IV disease who were rendered free of macroscopic disease by surgery or radiation therapy) or in patients with oligometastatic disease (patients with stage IV disease in whom all known macroscopic tumour can be resected or irradiated) [14]. This, of course, makes sense because we have known for many years that chemotherapy can sometimes cure microscopic disease, but rarely cures clinically manifest disease.

These clinical characteristics may allow us to restrict studies of high-dose therapy to patients with stage IV disease who may potentially achieve long-term survival, but this is probably true for conventional types of chemotherapy as well. What is needed are tests to predict which type of chemotherapy is best or which is useless for an individual patient. There appears to be some progress in this field as well. The Dutch study of high-dose chemotherapy in the adjuvant treatment of breast cancer has found that patients with HER2/neu-positive tumours derive no benefit from high-dose therapy, but those with HER2/neu-negative tumours do [15]. This observation confirms the conclusions of several retrospective studies that HER2/neu-positive tumours should probably not receive high-dose alkylating chemotherapy. In addition, if one assumes that 20–25% of patients in a randomised study have HER2/neu-positive disease, that these patients will not benefit from high-dose therapy and will in fact do worse if effective anthracycline-based therapy is withheld, than any benefit of high-dose therapy for the HER2/neu-negative tumours will be invisible in the study outcome. This elegantly explains the apparently negative results of some randomised studies with non-symmetric study designs [16].

Finally, it is hoped that modern technology, for instance employing DNA microarrays, could help in identifying tumours that would benefit from specific chemotherapeutic agents. Tentative gene expression signatures predicting taxane-sensitivity have already been reported [17]. High-dose chemotherapy with autologous peripheral blood progenitor cell transplantation has become a safe and reasonably well-tolerated treatment modality that can even be administered in the outpatient setting. Now that standard chemotherapy treatment costs have increased dramatically due to the price of agents such as trastuzumab and docetaxel, it can no longer be viewed as excessively expensive. Our expanded armamentarium, which in addition to high-dose chemotherapy includes taxanes, capecitabine, trastuzumab, dose-dense chemotherapy, third-generation aromatase inhibitors and a range of novel drugs in the pharmaceutical pipeline, provides a strong rationale to re-evaluate our ability to cure patients with limited stage IV breast cancer. The development of intelligent clinical trials with such an objective, that build on our knowledge of tumour biology and that may even expand it, is a major challenge for medical oncologists in the first decade of this century.

Conflict of interest statement

None declared.

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