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High Dose Chemotherapy with Haemopoietic Support for Breast Cancer

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INTRODUCTION

APPROXIMATELY 100 000 women die each year in Western Europe and North America as a result of breast cancer. Despite the discovery of new cytotoxic agents which have activity in this disease, the prognosis for metastatic breast cancer has not altered significantly in the past 50 years, with a median survival from detection of 16–18 months. Clearly, the discovery of new therapeutic approaches remains a priority.

Breast cancer is a chemosensitive malignancy, with high response rates being documented to a variety of agents when given as first-line therapy. Unfortunately, drug resistance develops, and responses to second-line therapy are less common and, when they occur, of brief duration. A potential mechanism for overcoming resistance is to increase the dose or dose intensity of delivery of chemotherapy. Such strategies could theoretically overcome potential mechanisms of resistance, including low drug delivery to the cell from pharmacokinetic causes (e.g. rapid clearance or de-activation), insufficient drug uptake across the cell membrane, and rapid inactivation or efflux of the drug from the cell (e.g. from increased expression of P-glycoprotein). There is good scientific rationale from *in vitro* and animal models to suggest that there is a dose–response relationship for many cytotoxic drugs against a variety of breast cancer cell lines [1], and several clinical studies have investigated whether this relationship exists in humans.

CLINICAL EVIDENCE OF DOSE–RESPONSE RELATIONSHIP IN BREAST CANCER

The earliest analysis of the relationship between dose and outcome in breast cancer was performed by Bonadonna and Valagussa in Milan [2]. They retrospectively divided patients who had received adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) into three groups according to the percentage of optimal dosage they had actually received. Patients administered >85% of the full cumulative dose had a significantly better disease-free survival than those receiving <65%, and this translated into a survival benefit which has been retained with prolonged (>10 years) follow-up. At least 11 analyses have been performed by other groups, but only four have been able to show a correlation between dose and outcome. Hryniuk and Levine devised a method for measuring dose intensity rather than total dose delivered, and retrospectively abstracted information from published series of adjuvant chemotherapy [3]. There was a highly significant correlation between dose intensity and 3 year disease-free survival in the 6106 patients included in the analysis. When data from trials of metastatic disease were assessed, dose intensity correlated significantly with the likelihood of achieving a response and this, in turn, was related to median survival [4]. Several criticisms can be made of these retrospective series, one of the main problems being that the groups who received higher or lower doses/intensities of chemotherapy may have differed in terms of their distribution of prognostic variables, i.e. common factors led both to the ability to tolerate less chemotherapy and to having a poorer prognosis. A detailed critique of the methodological problems associated with these analyses in breast cancer has been published by Henderson and associates [5].

A more reliable method of assessing the potential value of dose in breast cancer is a prospective, randomised study comparing two or more dose levels of cytotoxic chemotherapy. To date, at least 14 such studies have been published, reviewed by Pinedo [6], the majority employing CMF or single agent doxorubicin. Unfortunately, all include relatively few patients, the largest having only 283, and they were designed with very small increments between the "low" and "high" dose arms, the maximum dose difference being only 3-fold. It is also important to note that, in most studies, the "high" dose arm utilised what were actually maximum standard doses so that the comparison is better described as between "full" dose and "low" dose therapy. Four trials show significantly higher response rates and survival for the higher dose arm, but the improvements were only modest. As there are often wide interpatient variations in serum drug levels at a given dose (up to 5-fold), there is likely to be marked overlap of serum levels between the two arms of these trials given the small dose increments employed. It is perhaps surprising that any differences in outcome were actually measured. These randomised trials suggest that if dose intensity of chemotherapy, in the narrow range tested, is important, its effect on survival is only modest.

HIGH DOSE THERAPY

Several studies have attempted to take advantage of the dose–response relationship observed in preclinical models by increasing the amount of chemotherapy delivered and protecting against the major dose-limiting toxicity—myelosuppression—using either haemopoietic growth factor support or progenitor cell rescue. The latter is derived either from bone marrow or peripheral stem cell harvest. As can be seen from Table 1, for most agents the dose increment which can be achieved by adding bone marrow rescue is rarely more than 2-fold greater than the maximally tolerated dose without support. Once doses above

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Table 1. Maximal doses (mg/m²) of single agent chemotherapy

Agent	Conventional dose	Max dose (no rescue)	Max dose (+ rescue)	Limiting extra-medullary toxicity
Cyclophosphamide	2000	8000	8000	Cardiac
Carmustine	200	600	1200	Pulmonary, hepatic
Melphalan	40	120	200	GI, hepatic
Etoposide	360	1200	2400	GI
Ifosfamide	5000	8000	18 000	Renal, bladder
Thiotepa	50	180	1135	CNS, GI
Carboplatin	400	1600	2000	Hepatic, renal

CNS, central nervous system; GI, gastrointestinal.

these levels are administered, other toxicities, predominantly gastrointestinal, become dose-limiting.

HAEMOPOIETIC GROWTH FACTOR SUPPORT

Several studies have investigated the potential to increase dose-intensity of single agent and combination chemotherapy using either granulocyte- or granulocyte-macrophage–colony stimulating factors (G-CSF and GM-CSF, respectively). The majority have shown the feasibility of this approach, and have reported high response rates, but there is no information on relapse-free and overall survival. The first study to be published utilised single agent doxorubicin with G-CSF given between courses [7]. For a control group of patients who received no growth factor, the maximally tolerated dose intensity of doxorubicin was 75 mg/m² every 3 weeks whereas dose intensities up to 150 mg/m² 2-weekly (a 5-fold escalation) were administered under G-CSF cover. All patients at dose levels above 100 mg/m² responded to therapy, but non-haematological toxicity, particularly epithelial, became severe at $\geq$125 mg/m². Randomised trials comparing regimens of dose-intensified chemotherapy (plus growth factors) with standard therapy are ongoing in several centres.

HIGH DOSE THERAPY WITH HAEMOPOIETIC PROGENITOR CELL SUPPORT

In order to take full advantage of the potential dose–response relationship of chemotherapy and radiotherapy, a large number of studies have been performed using myeloablative regimens followed by rescue, initially with autologous bone marrow (ABMR), and more recently with progenitor cells derived from peripheral blood (PBPC). The latter technique reduces the morbidity of the procedure and, in particular, decreases the duration of thrombocytopenia [8], but does not allow greater doses of chemotherapy to be given. When combination regimens are chosen, individual agents should ideally be independently active against breast cancer, show a steep dose–response curve, be non-crossresistant and have non-overlapping non-haematological toxicity. High dose therapy has been employed in four main settings:

(i) for metastatic disease which is primarily refractory to chemotherapy
(ii) for metastatic disease as first-line therapy
(iii) for metastatic disease as "consolidation" after response to first-line standard chemotherapy
(iv) for high risk patients in the adjuvant setting.

To date, the published results in all settings have come from single arm studies, and no randomised comparisons between high dose therapy and a control arm have been completed.

HIGH DOSE THERAPY FOR REFRACTORY METASTATIC BREAST CANCER

At least 50 studies have included women with advanced breast cancer which had either progressed during standard chemotherapy or failed to respond. Approximately half of these studies have employed single agent chemotherapy, predominantly with alkylating agents, and six have combined chemotherapy with total body irradiation (TBI). Eighty per cent of the studies included less than 10 patients. Using pooled data from 366 patients in all published series, Sledge and Antman [9] demonstrated that, in this setting, combination chemotherapy was associated with higher response rates (OR 69% [95% CI, 63–75%], CR 17% [95% CI, 12–22%]) than single agents (OR 29% [95% CI, 21–37%], CR 5% [95% CI, 1–9%]) and that the addition of TBI (OR 63% [95% CI, 38–84%], CR 37% [95% CI, 16–62%]) may have improved the percentage with complete remission. The fact that responses to high dose therapy were seen despite progression on previous conventional doses suggests that a dose–response effect may exist. Unfortunately, the value of the responses appeared small with very short median durations, when quoted, averaging only 4 months approximately.

HIGH DOSE THERAPY AS FIRST-LINE TREATMENT FOR METASTATIC BREAST CANCER

The use of high dose therapy as initial treatment has the theoretical benefit of reducing the chance of emergence of resistance which could occur with prior exposure to several cycles of conventional dose therapy. There have been four studies employing this approach with a total of 53 patients, reviewed by Peters and associates [10]. The overall and complete response rates were 75% (95% CI, 62–86%) and 47% (95% CI, 33–47%), respectively, with median survival times of 14–18 months. These results are not significantly different from the results of conventional dose regimens, although in each study a small number of patients (approximately 20%) remained in continuous complete remission for more than 3 years. The degree of toxicity was high, with 10% overall procedure-related deaths.

HIGH DOSE THERAPY AS "CONSOLIDATION" FOR METASTATIC BREAST CANCER

The theoretical benefits of using high dose therapy after an induction regimen are that pretreatment reduces the tumour volume and may decrease the number of cells which are resistant

to the high dose agents. Perhaps most importantly, this approach allows selection of those patients with tumours which are sensitive and who are likely to benefit from use of consolidation therapy. Twenty studies have been reported in the literature with over 340 patients in total. For all patients, the average overall response rate after induction chemotherapy was 80% (95% CI, 76–84%) (CR 30% [95% CI, 25–35%]) and high dose therapy increased the number of CRs so that, after all treatment, the CR rate was 58%. Only half of the studies included more than 10 patients and a detailed analysis of these has been performed by Eddy [11] and the results compared with published series of patients who received conventional chemotherapy. Although the response rates did appear higher when consolidation therapy was given, the median response duration was calculated at only 6.6 months compared with 9.7 months for standard chemotherapy. Given the 9% overall procedure-related mortality, the conclusion was reached that high dose therapy as consolidation for metastatic breast cancer has not been shown to confer any obvious benefit. The high levels of patient selection inevitable in such small studies, together with the generally poor reporting of response duration and survival, and limited reporting of toxicity and quality of life, make them difficult to interpret. A prospective randomised trial comparing "consolidation" with standard therapy is warranted to properly determine the clinical value of this approach, particularly with the observation by authors of each study that a small number (approximately 25%) of those achieving complete remissions have responses which appear durable and were ongoing at the time of reporting with follow-up of 2–4 years. Four such trials are ongoing and their importance has been increased by an assessment by Peters and Rosner [12] of the economic cost of high dose therapy in this setting. They estimate the cost per year of life extended by high dose chemotherapy to be $73 300 compared with $31 500 for conventional chemotherapy.

HIGH DOSE ADJUVANT CHEMOTHERAPY

The use of high dose chemotherapy in the adjuvant setting has been the subject of a large amount of clinical research over the past decade and the recent results from a study by Peters and colleagues [13] from Duke University have engendered considerable optimism among oncologists. A group of women who have a particularly poor prognosis following mastectomy can be clearly defined by the extent of axillary lymph node involvement, and for those with more than ten positive nodes there is almost a 90% chance of relapse by 10 years of follow-up. Adjuvant chemotherapy using low-dose outpatient regimens has been demonstrated to produce modest but consistent improvements in disease-free and overall survival. If a dose–response relationship does exist for breast cancer, the use of high dose regimens with haemopoietic rescue would be particularly appropriate in the adjuvant setting, given the low tumour volume which is present in such patients and the lack of exposure to previous chemotherapy, both factors contributing to a reduced chance of the prior development of resistance. A further factor which makes the adjuvant setting more favourable for the use of high dose therapy is that patients generally have a better performance status than those with metastatic disease, and they, therefore, tolerate the side-effects more easily, reducing the risk of procedure-related mortality. The Duke study included 102 patients, all with $\geq$10 positive axillary nodes at the time of mastectomy, who received four courses of cyclophosphamide, doxorubicin, 5-flourouracil (CAF). Autologous bone marrow was stored from all patients and, as the study progressed, peripheral stem cells were also collected. 85 patients subsequently received a high dose regimen of cyclophosphamide, cisplatin and BCNU followed by haemopoietic rescue. The Kaplan–Meier estimate for the probability of any local or systemic relapse at 30 months was only 19% and an updated analysis with a minimum of 2.2 years follow-up showed that no event had occurred after 28 months. Comparison was made with three historical or concurrent CALGB adjuvant chemotherapy trials in which the event-free survival at 2.5 years was only 38–52%, significantly worse than the high dose group. There was, however, a high treatment-related mortality of 12% in the Peters series and the cost of each procedure was considerable at an average of $88 836. Two other series on the use of high dose therapy with bone marrow/stem cell support in women with $\geq$10 positive axillary nodes have been published with results which are similar to those of Peters. Of the 18 patients treated by Tajima and associates [14], 67% remained disease-free at a median follow-up of 41 months. Gianni and associates [15] treated 48 patients, and disease-free survival at a median follow-up of 21 months was 93% compared with 43% for concomitant but non-randomised controls receiving conventional therapy. While the results are encouraging, these were small studies containing highly selected patients, and comparisons of outcome with non-randomised controls is frequently misleading. The implications for healthcare systems of the widespread use of such a costly and resource-intensive therapy are enormous, and it is obviously essential to determine the exact value of high dose treatment in this patient population before accepting it as a standard approach. Eleven prospective randomised trials comparing conventional adjuvant chemotherapy with a variety of high dose regimens have been established, but it will be some years before their results will be available.

FAILURE OF HIGH DOSE THERAPY

Even with high dose therapy and haemopoietic support, the majority of patients treated will die. Procedure-related toxicity has accounted for up to 15% of deaths in some series. However, this figure has fallen significantly with the widespread availability of myeloid growth factors and peripheral stem cell support, together with modifications of some of the conditioning regimens of chemotherapy. It is possible that failure occurs because, even with these higher doses of chemotherapy, the amount of drug delivered is still too low. A recent study [16] has attempted to increase cytotoxic exposure in patients with metastatic disease by administering "double dose-intensive" chemotherapy using melphalan with stem cell rescue followed, at the time of neutrophil recovery, by high dose cyclophosphamide, thiotepa and carboplatin with autologous bone marrow and peripheral stem cells. The regimen was feasible with no procedure-related mortality being recorded, and will now be studied for activity in a larger number of patients. A further potential reason for the frequency of recurrence after high dose therapy is the reinfusion of tumour cells with the bone marrow or peripheral blood progenitor cell harvests. Unfortunately, bone marrow is one of the most common sites for metastasis of breast cancer, and recent detailed analyses of marrow samples [17] have revealed that even for stage I disease, there is a 25% incidence of involvement. This figure increases to 50% taking all stages together. Attempts to remove tumour cells by *in vitro* purging have not been successful, and damage to normal progenitor cells is significant. More recently, positive selection of CD34 and other primitive haemopoietic cells has become possible with the availability of selection devices such as the Baxter and CellPro

columns and AIS panning flasks. One clinical study, using this technique to treat autologous marrow prior to reinfusion after high dose therapy in breast cancer, has already been published [18]. It has shown the technique to be feasible and, encouragingly, to result in 1–4-fold log reductions in marrow tumour cell contamination.

CONCLUSIONS

There is good evidence from preclinical and animal models that a dose–response relationship to chemotherapy exists for a variety of breast cancer cell lines. Attempts to capitalise on this in the hope of improving outcome in patients is a logical approach. Confirmation of a dose–response relationship in humans has largely relied on retrospective analyses, and has been confounded by several methodological problems, while prospective studies have randomised patients to receive only small differences in dose-intensity for the "high" and "low" dose arms. At best, the results suggest that, within the ranges tested, a small dose–response relationship may exist. What is more clear from these studies is that reductions of dose below standard levels, for whatever reason, are associated with a worse outcome.

High dose therapy with rescue has now been studied in the advanced and adjuvant settings in several small uncontrolled studies. It seems clear that for women with metastatic disease which fails to respond or progresses on primary standard chemotherapy, high dose therapy produces, at best, only transient responses with unacceptable toxicity. In this setting, further trials would not appear justifiable without new drugs or a new approach. For those who have responsive metastatic disease, high dose therapy increases the number who achieve complete remissions and a small proportion of these will have durable responses lasting more than 2 years. Given the relatively marginal nature of the benefits of this approach, the associated morbidity and mortality and high financial cost, its value should be properly examined in the currently ongoing randomised prospective trials. This should occur before centres not participating in these trials treat such patients with high dose therapy. The potential value of high dose chemotherapy appears to be greater in the adjuvant setting, with encouraging data suggesting prolonged disease-free survival compared with standard dose regimens. Again, no randomised prospective studies have confirmed the value of this approach and, until the results of ongoing trials are available, its use should not be accepted as standard therapy.

A continuing programme of research in this field is necessary. Already the morbidity and mortality of high dose therapy has been reduced with the availability of peripheral progenitor cell and colony stimulating factor support. New approaches, including the use of *ex vivo* cell selection, progenitor cell expansion and double (or more) course therapy are being tested.

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