

Special article

Dose effect relationship in breast cancer

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H. M. Pinedo

Department of Oncology, Free University Hospital, Amsterdam, The Netherlands

Introduction

Breast cancer is the leading cause of death among solid tumors in women. While treatment with standard doses of chemotherapy is potentially curative in leukemias, lymphomas, testicular cancer and childhood solid tumors, conventional chemotherapy has, as yet, no curative impact on advanced breast cancer [1]. On the present occasion, I wish to review some recent clinical developments in the area of dose effect relationship and their implications on the prognosis for breast cancer patients. I will refer to the literature and to some of the work that has been performed at The Netherlands Cancer Institute and at the Free University Hospital in Amsterdam. In both institutes clinical research has focused in the past on better understanding of mechanisms of clinical drug resistance, which preclude desired effects of chemotherapy.

Theoretical background of dose-response relationship

Apart from primary and acquired cellular drug resistance, the efficacy of chemotherapy in solid tumors is limited by high intratumoral interstitial pressure. This is caused by increased leakiness of tumoral capillaries and by the absence of lymphatic capillaries, leading to an efflux of drugs from the tumor to extratumoral tissues [2]. Since capillaries are mainly located in the outer layer of solid tumors the peripherally located cells are exposed, although briefly, to a much higher concentration of drugs than those in the core of the tumor. Moreover, the low blood flow in the vascularized necrotic central region often results in hypoxia, thereby preventing those molecules that do arrive at the core of the tumor from functioning successfully. We may, however, have discovered some tools to circumvent a number of these obstacles in tumors with moderate chemosensitivity, including breast cancer.

One way to improve the efficacy of chemotherapeutic agents in solid tumors is to increase the dose of the drug in order to achieve a deeper penetration of the

tumor. By increasing the dose, you increase the concentration to which cells will be exposed; penetration does not change. In doing so we create a higher local extracellular and intracellular concentrations resulting in increased cell kill. In addition, we must apply the optimal combination of drugs that can be used at such high doses [3]. Suitable agents for high dose combination chemotherapy are those which:

1. are independently active in a particular disease,
2. show a steep dose-response curve,
3. are non-cross resistant and
4. have non-overlapping non-myelosuppressive toxicity [4].

A number of alkylating agents meet these criteria. Formerly alkylating drugs were supposed to be all cross-resistant, but it is now becoming clear that this concept is wrong. Schabel et al. [5] showed lack of cross-resistance among drugs pertaining to the group of alkylating agents. For example, simultaneous exposure of a human breast cancer cell line to thiotepa and cyclophosphamide showed remarkable in vitro synergism [6]. Also, cisplatin and carboplatin are alkylating agents for which a steep dose response curve has been proven to exist in vitro [4]. The curve of carboplatin is slightly less steep than that of cisplatin [7, 8]. It has been shown that the number of platinum-DNA adducts increases with in vitro exposure of cells to higher doses of these drugs [9]. As the anti-tumor activity of platinum analogs is thought to be a result of the interaction with DNA we are currently studying the degree to which anti-tumor response and the number of these adducts correlate in vivo. Despite the somewhat shallower curve of carboplatin, its reduced non-myelosuppressive toxicity offers many advantages over cisplatin for high dose studies. The increase in dose that can be achieved in vivo with carboplatin is definitely greater than that for cisplatin. Finally, conventional doses of cisplatin and carboplatin have shown some activity in advanced breast cancer. Still there is very limited information on the dose effect relationship of any single alkylating agent in the clinical setting, in spite of the fact that there has been analysis of combination chemotherapy.

Clinical research on dose-response relationship

The first analysis of the dose-response relationship for conventional adjuvant combination chemotherapy in post-menopausal patients with breast cancer was performed by Bonadonna and Valuggusa in 1981 [10, 11]. The effects of actually administered doses of cyclophosphamide, methotrexate and 5-FU (CMF) were, in retrospect, compared with those of standard adjuvant chemotherapy. The group receiving the highest dose, i.e. >85% of the planned CMF dose, showed a significantly improved disease-free and overall survival over controls, but patients in whom dose reduction had been applied had no benefit from the treatment [11].

In metastatic disease studies on dose-response effect of conventional combination chemotherapy showed some survival benefit [12, 13]. The majority of trials in which the actually delivered dose differed significantly from that in the low dose arm showed higher response rates for the higher dose arm (Table 1) [14].

Strategies to overcome dose-limiting toxicity

The application of the steep dose-response concept for alkylating agents in the clinic has been hampered for many years by dose limiting bone marrow toxicity. However, hematopoietic support with growth factors and/or stem cell transplantation now offers new possibilities to push doses up to levels where non-myelotoxic side effects become dose-limiting. For the purpose of this presentation I define high dose chemotherapy as the highest dose which can be administered with the

Table 1. Randomized studies of dose intensity without hematopoietic support in breast cancer.

Stage/prior treatment	No. pat.	Regimen	Response rate - %		Reference
			LD	HD	
IV/None	113	CMF	11	30	Tannock et al., 1988 [13]
IV/None	283	CMFVP	40	59	Hoogstraten et al., 1976 [57]
IV/None	165	CMF +/-	57	63	Tormey et al., 1982 [58]
IV/None	60	FAC x 3	39	70	Malik et al., 1982 [59] & Hortobagyi et al., 1987 [60]
IV/Limited	103	CMF	32	50	Beretta et al., 1986 [61]
IV/Limited	103	DOX	32	30	O'Bryan et al., 1977 [62]
IV/Extensive	68	DOX	6	24	O'Bryan et al., 1977 [62]
IV/Extensive	37	CDDP	0	21	Forastiere et al., 1982 [63]
IV/Extensive	23	CDDP	0	0	Samal et al., 1978 [64]

From Antman et al., J Clin Oncol, 1992 [14].

use of hematopoietic growth factors without stem cell support. By using autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation (PSCT) to overcome prohibitive myelotoxicity, further dose escalation appears feasible [15]. The very high dose of chemotherapy which can be tolerated with additional support of such hematopoietic stem cells will be referred to as megadose chemotherapy. Megadose chemotherapy with the use of AMBT has considerable toxicity, with a mortality of 10%–20%, and is extremely expensive [16]. The newly developed method to harvest peripheral stem cells has really determined a breakthrough, as stimulation of hematopoiesis results in a shift of hematopoietic stem cells from the bone marrow into the peripheral blood. This mobilization can be triggered by conventional chemotherapy and/or by hematopoietic growth factors. At The Netherlands Cancer Institute, Richel et al. [17] mobilized peripheral stem cells with a modified FEC regimen (500 mg/m² 5-FU, 120 mg/m² epidoxorubicin, 500 mg/m² cyclophosphamide followed by G-CSF 300 µg/d on days 1–11). The drugs were administered on a single day. Peripheral stem cells were harvested during two to three leucopheresis sessions, on days 7–9 following FEC. The CD34 antigen, a glycoprotein expressed on early hematopoietic progenitor cells, was used to identify the stem cells in the peripheral blood [18]. CD34⁺ positive cells are early hematopoietic progenitor cells and appear morphologically like lymphocytes. After mobilization and harvesting these stem cells from the blood, they are returned to the patient shortly after administration of megadose chemotherapy in order to reduce its severe myelosuppression. The advantages of PSCT over ABMT are faster recovery of marrow function [19, 20], reduced morbidity and probably mortality and lower cost.

Selection of high risk patients for dose intensification

In further studies careful selection of patient subgroups will be important. Indications should include patients with primary breast cancer in the very high risk category with a more than 80% chance to develop metastases, since the impact of conventional adjuvant chemotherapy is limited in this setting. Thirty-one randomized trials, studying the effect of systemic adjuvant treatment have recently been evaluated in a meta analysis including 11,000 patients with early breast cancer [21, 22]. Both combination chemotherapy and tamoxifen clearly showed a reduction in recurrences and mortality. There is a correlation between the number of tumor positive axillary lymph nodes and the chance of treatment failure [23]. A sharp fall in the 5-year relapse free survival (RFS) rate from 57% to 30.5% occurs in 4+ node positive patients [24]. In the group of 13+ positive nodes the 5-year RFS rate is as low as 16% [19]. Similarly, 5-year RFS in patients with a tumor-positive apical axillary lymph node, is only 12% following conventional radiotherapy. It is obvious that

patients with positive subclavicular nodes also belong to this poor-risk category. Indeed, several centers still include biopsy of subclavicular nodes in their diagnostic staging working in order to identify this very high-risk group of patients who are then offered primary radiotherapy instead of surgery. Such patients usually do not receive adjuvant chemotherapy. In the meantime, a dose-effect relationship of adjuvant chemotherapy within the conventional dose range has been shown [25, 26], and a number of phase II studies of adjuvant megadose therapy in very high risk groups [27, 28] have now been initiated. As yet time does not permit conclusions. However, some encouraging results are emerging. Marks et al. performed a phase II study of megadose adjuvant consisting of 4 courses of standard dosages of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) followed by megadoses of cyclophosphamide (5625 mg/m²), cisplatin (165 mg/m²) and carmustine (600 mg/m²) plus ABMT in 49 patients with 10+ positive lymph nodes. Among the first nine patients who were not given post-operative radiotherapy (it was felt that megadose chemotherapy might eliminate any microscopic local residual disease in these cases) three developed a local recurrence. In the 40 patients treated thereafter local radiotherapy (60 Gy) was added to the new adjuvant treatment, and this group showed only two local recurrences [29]. Thus, even with such high doses it appears that radiotherapy is required in high-risk patients to prevent local recurrence following mastectomy.

So far, no randomized study on megadose adjuvant chemotherapy has been completed on such patients. The Milan Group is currently performing a randomized study on patients with 10+ lymph nodes, while investigators in The Netherlands are performing two randomized trials. The Netherlands Working Party on Autotransplantation is investigating the effect of megadose vs. conventional doses of chemotherapy in patients with 4+ nodes. Following surgery, patients are randomized between 5 courses of conventional FEC or 4 courses of FEC plus one course of CTC megadose chemotherapy consisting of cyclophosphamide (6 g/m²), thiotepa (480 mg/m²) and carboplatin (1.6 g/m²) plus PSCT. All patients receive post-operative radiotherapy and adjuvant tamoxifen. In another study, performed at The Netherlands Cancer Institute, a similar regimen is used in patients with positive subclavicular lymph nodes. However, treatment is initiated in both arms with three cycles of FEC with an increased dose of epirubicin (120 mg/m²). Following mastectomy all patients receive a fourth cycle of FEC to be continued by either megadose CTC plus PSCT and radiotherapy or by radiotherapy alone. All patients receive tamoxifen. Follow up is still too short for conclusions.

At the Free University Hospital research interest has concentrated on high dose chemotherapy with GM-CSF in patients with locally advanced breast cancer (LABC). LABC is defined according to the 1978 UICC TNM classification as a tumor of >5 cm with fixa-

tion to fascia and/or muscle (T₃) or direct extension to the chest wall or skin (T₄) [30]. Multimodality treatment of the primary tumor, combining conventional chemotherapy, surgery and radiotherapy (Table 2) results in less local recurrences than radiotherapy or surgery alone [7]. Three to four courses of chemotherapy render the tumor operable in >90% of non-inflammatory LABC patients. However, the 5-year DFS still appears to be only 20%, with most distant metastases developing within 2 years. In the case of inflammatory disease, where prognosis is even worse, this multimodality treatment has improved the 5-year survival rate from 1.9% or 2.4% for radiotherapy or surgery alone [31] to 23%–74% [32, 33]. Inflammatory breast cancer is a chemosensitive disease and a good test-case for the dose-effect concept. Gianni et al. treated six patients with inflammatory breast cancer with a single course of high dose cyclophosphamide (7 g/m² d 1) plus intravenous recombinant human granulocyte macrophage colony stimulating factor (GM-CSF) (5.5 µg/kg/d, d 1–14) [34]. No stem cells were given. Responses were evaluated after one month and included one CR (17%) and five PR's (83%). With GM-CSF the median time to reach an absolute neutrophil count of >500/µl was 13 days, differing significantly from the 19 days observed in the control group (*p* < 0.001). The platelet count recovered to above 100,000/µl by day 14 in patients receiving GM-CSF vs day 16 in the control group (*p* < 0.004).

In the study at the Free University Hospital eight patients with LABC underwent high dose treatment consisting of doxorubicin (90 mg/m²), plus cyclophosphamide (1000 mg/m², every 21 days) followed by GM-CSF (250 µg/m²/d, d 2–11, sc or iv) (HDAC) [8]. In case of a partial or complete response, surgery and post-operative locoregional irradiation were performed. In our experience subcutaneous (sc) administration of GM-CSF results in a more rapid recovery of neutrophils and platelets than continuous i.v. infusion. In addition, patients treated with sc GM-CSF experienced less non-hematological toxicity compared to i.v. [35]. Among the eight patients with LABC we observed 3 CR's and 5 PR's. Despite a rapid tumor regression with responses already noted after one single course, histologic examination after surgery always showed foci of viable tumor cells. Considering

Table 2. Site of relapse following CA after megadose chemotherapy.

Author	Site of relapse				
	No. of patients	No. of relapse	Prior site	Prior + new alone	New
Kennedy [45]	24	20	19	10	1
Williams [48]	2	14	14	0	0
Peters [53]	22	12	11	0	1
Livingstone [43]	30*	22	17	1	4 (3CNS)

* including 23 hemibody irradiation.

the observations of Marks et al. it is not surprising that high dose chemotherapy with growth factor support fails to eradicate all cells of the primary tumor in LABC. In summary, post-operative radiotherapy is recommended as part of the multi-disciplinary approach to LABC.

Patient selection in metastatic disease

Selection of patients for studies of the dose-response concept is even more difficult for cases with metastatic disease. This disease remains essentially incurable, with a consistent median survival of only 2 years [36, 37]. Overall, the 5-year survival rate is 21%. Although chemotherapy regimens containing anthracyclines show higher response rates than regimens lacking these drugs [38, 39], they fail to affect the cure rate. In order to observe occasional cures one requires a higher complete response rate than the 10%–20% [13] achieved with the present regimens. Moreover, the median duration of CR's presently achieved does not exceed 1 year [14, 16].

In an attempt to improve treatment results in metastatic breast cancer Bronchud et al. increased the dose intensity of doxorubicin in 15 patients, using sc granulocyte colony stimulating factor (G-CSF) [40]. Treatment of eight patients with 3 bi-weekly cycles of 75–100 mg/m² doxorubicin resulted in one CR and four PR's, while seven patients who received 125–150 mg/m² doxorubicin experienced four CR's and three PR's. Administration of G-CSF speeded up recovery of absolute neutrophil count to values above 1,000 from day 15 to day 9. Median time to progression of disease was only 6 months (range 2–9 months).

At the Free University Hospital ten patients with metastatic disease received HDAC every 3 weeks, the same regimen which was given to LABC, showing two CR's and six PR's. Although the two studies show encouraging response rates, the duration of response remains short. The data show that doxorubicin is not the ideal drug to prove the dose-response concept because of the limited increase in dose feasible due to non-hematological toxicity.

Untreated stage IV patients: Megadose chemotherapy upfront?

A quantum leap has been introduced with the introduction of megadoses of alkylating agents plus ABMT in metastatic breast cancer responding to conventional chemotherapy [41, 42]. Here, conventional chemotherapy has been purposely used as induction therapy to reduce the tumor bulk and allow for selection of chemotherapy-sensitive tumors for intensification with megadose chemotherapy plus ABMT [14, 20, 43–47]. Antman et al. reported 29 patients with metastatic disease who, showing response to conventional chemo-

therapy, received megadose cyclophosphamide, thiotepa and carboplatin plus ABMT. Ten out of twenty-nine patients achieved CR with conventional doses. The remaining patients had a PR. The replacement of conventional chemotherapy by megadose treatment resulted in a total of 17 CR's (59%). Time to treatment failure for those in CR (19 months) was higher than for those in PR (5 months) [14], and longer than that observed for CR's obtained with conventional doses of chemotherapy.

Williams reported 9 out of 14 PR's converted into CR [48], while intensification of chemotherapy increased the CR rate from 38% (after induction) to 64% in a study by Jones et al. [49] in 44 previously untreated patients with metastatic disease. Thus, megadose appeared to convert many PR's into CR's.

A slightly different approach has been followed by de Vries et al. in a national phase 2 study in The Netherlands. Nineteen patients with metastatic disease, who had achieved a CR on any conventional regimen were treated with megadose chemotherapy consisting of 180 mg/m² melphalan (d 1–3), 60 mg/m² mitoxantrone (d 1–2) and ABMT. Afterwards all patients received radiotherapy at sites of prior bulky disease. This is a very logical approach considering the findings at mastectomy following chemotherapy for LABC. Despite the encouraging observations I wonder whether the aim of a protocol starting with several cycles of conventional chemotherapy to be followed by megadose is correct as the patient may be left with clones of cells which are by then also resistant to megadoses of chemotherapy. We know that cells may develop resistance after short term exposure to drugs. A more rational approach would be to apply megadose chemotherapy upfront in previously untreated patients with metastatic disease [48, 50–54]. Indeed, tumor regression with megadose chemotherapy appears to be rapid under such circumstances, with PR's achieved in 11 days (median) and CR in 12–18 days (median) [53, 55]. The latter studies showed a CR rate of 30%–50%, of which 10%–20% were still in CR at 2 to 3 years after treatment [16]. Of 22 patients treated with megadose chemotherapy plus ABMT for metastatic disease [50] 3 are still in continuous CR at 6.3, 7.6 and 7.3 years [Peters WP, personal communication]. All these small studies on megadose chemotherapy in advanced disease have given promising results and warrant randomized trials to evaluate their superiority in various subgroups of patients with breast cancer.

Influence of site of relapse on treatment strategies

Detailed information is available on the site of relapse in lymphoma patients. In 76% of patients with non-Hodgkin's lymphoma treated with megadose chemotherapy plus ABMT, the site of relapse was at the initial site of disease [55]. The correlation between pretreatment sites of disease and sites of initial recurrence in

patients with Hodgkin's disease following MOPP treatment is exceptionally strong [56]. A similar pattern has been reported for breast cancer [43, 45, 48, 53]. Among 12 patients with metastatic breast cancer who relapsed after megadose chemotherapy plus ABMT, only 1 patient suffered from a relapse at a new site. Predominant sites of relapse were sites of pretreatment bulky disease > 3 cm [53]. Livingstone et al. reported 4 out of 22 patients who relapsed at a new site. Of these four, three had a relapse in the brain (Table 3) [43]. Three out of ten patients with metastatic breast cancer in the study of Hoekman et al. at the Free University relapsed at a new site. All three experienced a relapse only in the brain or cerebrospinal fluid. The others relapsed at a site of prior bulky disease. A similar pattern of relapse was observed following treatment for LABC, where two out of three distant relapses occurred in the CNS.

Many *in vivo* clues supporting the dose-effect concept for chemotherapy in breast cancer are present where a single course of mega- or high-dose rapidly removes macroscopic disease. It is also clear that one course will be unsuccessful in eradicating all tumor cells. The drugs do not reach the core of large metastases during the first treatment. So, not all patients treated with one cycle achieve a CR, while the majority relapse. Repeated treatment applying ABMT appears to be too toxic. However, PSCT is more successful in restoring bone marrow function following megadose chemotherapy and is rapidly gaining momentum. Repeated administration of megadose chemotherapy plus PSCT has already proved feasible at The Netherlands Cancer Institute and will probably become an important avenue in our attempts to improve results of chemotherapy in breast cancer.

Since most relapses occur at previous sites of disease and chemotherapy alone has proven inferior to multimodality treatment in LABC, another approach to be investigated systematically is the use of surgery and/or radiotherapy following megadoses of chemotherapy to treat sites of bulky disease which have gone into CR.

Conclusion

It is evident that increasing the cure rate for patients with advanced breast cancer will be extremely difficult, requiring complicated trials and a great deal of discipline. We will need randomized studies to evaluate the

Table 3. New treatment strategies for metastatic bulky sites after achieving complete remission with megadose chemotherapy.

Site of disease	Treatment options
Breast	Surgery
Thoracic wall	Radiotherapy/surgery
Liver	Surgery
Bone	Radiotherapy
Brain	Surgery/radiotherapy
CSF	i.t. chemotherapy

exact role of high-dose chemotherapy and that of megadoses of chemotherapy followed by PSCT, in both patients with high-risk primary breast cancers and in women with advanced disease.

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Correspondence to:

Prof. H. M. Pinedo
Dept. of Oncology
Free University Hospital
De Boelelaan 1117
1081 HV Amsterdam, The Netherlands