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ORIGINAL ARTICLE

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High-dose chemotherapy with hematopoietic rescue in breast cancer: from theory to practice

Abstract The development of more effective treatment strategies currently provides the only realistic hope of reducing breast cancer mortality. Among such treatments, high-dose chemotherapy (HDC) has been proposed to be a potentially curative strategy. Consideration of the factors involved in the successful treatment of human tumors suggests that HDC could be integrated into the treatment of breast cancer, but only if the treatment is adequately planned with regard to tumor kinetics and chemotherapy sensitivity and resistance patterns. Two randomized studies of the use of HDC in breast cancer have been published recently. In the first, HDC using a combination of cyclophosphamide, mitoxantrone, and etoposide as initial treatment was compared to a conventional dose regimen consisting of cyclophosphamide, mitoxantrone, and vincristine. The second study compared the effects of early or delayed HDC in patients who had an optimal response to conventional-dose induction chemotherapy. Both studies showed HDC to be more effective than conventional-dose treatment in delaying the time to progression, but only in the study in which HDC was used as the initial treatment was there an effect on survival. The differences between these two investigations can probably be explained on the basis of the different effects of the treatment regimens on tumor kinetics and the efficiency of HDC when used as salvage therapy in the delayed HDC group. Dose-intensive therapy has an established role in breast cancer. Attention now needs to focus on methods of optimizing this treatment strategy.

Key words High-dose chemotherapy · Breast cancer

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Introduction

Breast cancer has a high mortality rate despite the limited success arising from the introduction of screening and adjuvant or early systemic treatment programs. Current evidence indicates that at least 30% of all patients diagnosed as having breast cancer will die of the disease [23]. For patients with poor prognostic features at diagnosis (among which lymph node status remains the most important predictor of outcome) the mortality rate is even higher: 40–50% of patients with between 4 and 9 positive nodes will relapse [8], whereas the relapse rate for patients with $\geq$10 positive nodes is $>$70% [24].

Epidemiology data indicate that the incidence of breast cancer is increasing worldwide. This trend has been most noticeable in developed countries such as the United States, where the lifetime risk for the development of breast cancer is now approximately 12%. This indicates that breast cancer will be a major public health problem well into the next century.

During the past decade, enthusiasm for the use of high-dose chemotherapy (HDC) as part of the overall strategy of treatment has increased. Although there is some evidence to support this approach, the use of HDC remains controversial. The aim of this paper is to review the current state of knowledge in this therapeutic area.

Obstacles to the cure of cancer using chemotherapy

The ability of chemotherapy to effect cure in a number of malignant diseases is now beyond question. However, the factors that determine the curability of malignancy by chemotherapy are not well defined. Although most of the curable adult cancers fall into the category of hematological malignancies, the small but consistently observed [11] increase (on the order of 3–15%) in the long-term survival (cure) of patients with early breast cancer following adjuvant chemotherapy suggests that the response of breast

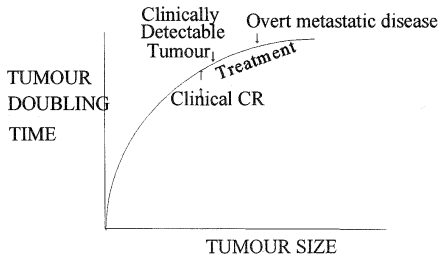

Fig. 1 Gompertzian growth kinetics

cancer cells to chemotherapy, at least at a certain stage of tumor growth, is not qualitatively different from that observed in hematological malignancies. Although the beneficial effects of adjuvant chemotherapy are currently modest, there is a general expectation that they can be improved. However, once recurrence or metastatic involvement is present, the disease is essentially incurable with current standard therapeutic approaches.

Two models have been advanced to explain the discrepancy between the potential curability of early-stage breast cancer and the essential incurability of overt metastatic disease. These two models may be termed the kinetic resistance and the cellular resistance models.

Kinetic resistance

The basic aim of chemotherapy is to reduce tumor burden through a cytotoxic effect on proliferating cells. However, the relationship between tumor proliferation and cytotoxicity and tumor regression is complex. Two hypotheses have been advanced to explain these relationships.

The first is the exponential model of tumor cell growth and cytotoxic effects, based mainly on the L1210 leukemia cell line and other experimental tumor models. The growth fraction, cell-loss fraction, and cell-cycle duration of the L1210 tumor line are remarkably stable. Skipper and colleagues [30] have shown that when such experimental tumors are treated with anticancer drugs a constant fraction of cells, for any given drug dose, are killed (log cell-kill). The exponential cell-kill hypothesis further states that each chemotherapeutic agent in a combination regimen will have its own log cell-kill, with the effects of the combination regimen thus being at least additive. The exponential cell-kill hypothesis has provided the rationale for the development of combination chemotherapy. Such combination therapy has proved to be remarkably effective in a number of clinical settings. However, the concept is probably simplistic when applied to human malignancy.

The growth of human cancers probably approximates more closely Gompertzian kinetics [14] (Fig. 1) than the Skipper-Schabel exponential growth model. In the Gompertzian model the tumor-doubling time is not constant as it is in the exponential model but rather decreases with increasing tumor size. This model predicts that proliferation is more rapid during the preclinical phase of tumor growth, with significant slowing of growth occurring by the time the malignancy has reached a clinically detectable size. Since cytotoxicity is related mainly to the growth fraction, the predictions from this model (Norton-Simon hypothesis [24–26]) suggest that the clinical response is associated with a relatively small reduction in total tumor burden and may be followed by rapid regrowth. This hypothesis suggests that a single-dose treatment, even in an aggressive chemotherapy treatment, may produce little real survival benefit.

For chemotherapeutic treatments to be curative there would appear to be a number of requirements. These include the availability of a regimen that produces a high complete response (CR) rate (i.e., optimal cytoreduction) and the delivery of a minimal number of courses of treatment, i.e., therapy is continued even after the achievement of a clinical CR to decrease the amount of tumor cells to a number below the minimal required for tumor regrowth. Even those tumors that are highly responsive to chemotherapy (e.g., gestational trophoblastic disease, Hodgkin's disease, and some of the acute leukemias) appear to require more treatment cycles than are required to achieve an apparent CR so as to effect cure.

The Gompertzian model has been used as the theoretical justification for the use of initial cytoreduction by conventional-dose chemotherapy followed by a single round of HDC or other "ablative" treatment as "consolidation" (cf. the current practice in bone marrow transplantation for leukemia and the current practice in HDC for breast cancer). However, the lessons drawn from the Norton-Simon hypothesis appear to be just as applicable to HDC regimens as to conventional-dose treatments. The challenge for the future will be to optimize high-dose treatment regimens such that therapy can be delivered repeatedly and as quickly as possible, but also in a manner that is safe and acceptable to the patient. These concepts will be further examined when the results of HDC trials in metastatic breast cancer are evaluated.

Cellular basis of drug resistance

Another factor that undoubtedly influences the success or failure of treatment is the existence of resistant subpopulations of cells in the tumor. Although some of the mechanisms responsible for cellular drug resistance (e.g., P-glycoprotein expression) have been defined in experimental tumor models, the clinical significance of P-glycoprotein expression remains unclear. Some investigations have demonstrated a relationship between P-glycoprotein expression and chemotherapy resistance [28]. However, studies from our laboratories have shown that although approximately 50% of tumors from patients with breast cancer express P-glycoprotein, positive immunostaining for this membrane protein has failed to predict anthracycline resistance [29], at least in first-line treatment for metastatic disease.

One approach to the problem of drug resistance, based on the Goldie-Coldman hypothesis [16], is the use of alternating non-cross-resistant combinations. Although

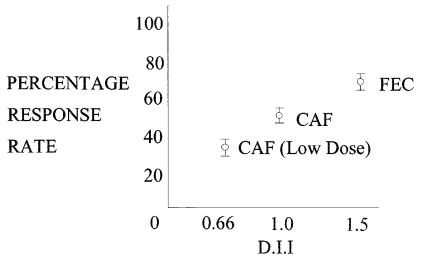

Fig. 2 Dose-intensive chemotherapy in breast cancer. CAF = cyclophosphamide + adriamycin + 5 fluorouracil; FEC = 5 fluorouracil + 4′Epiadriamycin + cyclophosphamide

this approach appears to have been successful in Hodgkin's disease, where a major factor may be the very high efficacy of both the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and the doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) combinations [6], there is no other clear indication that alternating therapy is any more successful than the use of a single, effective treatment schedule. In particular, there is no consistent evidence that tumors not previously curable by chemotherapy can be eradicated by the use of conventional-dose, alternating, non-cross-resistant chemotherapeutic treatment approaches.

It must also be remembered that the P-glycoprotein-mediated multidrug resistance (mdr) mechanism is not the only mechanism of drug resistance. Other cellular mechanisms include drug inactivation and DNA repair as well as pharmacological and pharmacokinetic effects. Although there is no definitive evidence, both kinetic and cellular resistance mechanisms are probably operative in metastatic breast cancer.

Clinical studies

Dose intensity and dose density

When the impact of these kinetic and sensitivity patterns on the clinical outcome of cancer treatment is considered, both drug-dose and temporal (treatment interval) considerations are relevant. The classic method of calculating dose intensity, developed by Hryniuk and Levine [17], treats all individual drug doses and the time factors as having equal weight. The dose intensity of a therapy is given by the sum of individual drug doses per unit time (drug 1 dose per square meter of body surface area + drug 2 dose per square meter + drug 3 dose per square meter); the dose-intensity index (DII) is obtained using the equation *DII* = [*drug 1 dose/m²*/cycle interval (*week*)] + [*drug 2 dose/m²/cycle interval*] + [*drug 3 dose/m²/cycle interval*]. When this method is applied (mostly retrospectively) to the analysis of various treatment regimens for advanced breast cancer (particularly to those including cyclophosphamide and/or doxorubicin) an approximately linear correlation between dose intensity and response is observed (Fig. 2).

Randomized clinical studies that support the concept of a dose-response effect in breast cancer include the studies of Tannock and co-workers [31], who investigated two different doses of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in women with metastatic breast cancer, and those of Bastholt and co-workers [2], who investigated four different doses of epirubicin. In both trials there was a significantly higher response rate at higher doses. In addition, in the Bastholt et al. study the time to treatment failure was significantly longer when epirubicin doses of 90–130 mg/m² were compared to doses of 40–60 mg/m².

In these studies, dose intensity was varied by dose manipulation, with the unit dose being given at the same treatment interval. An alternative approach would be to decrease the cycle interval (sometimes termed dose density). Both approaches result in an increased drug dose per unit time ratio, but whether they are equivalent is not clear.

A recent Cancer and Leukemia Group B (CALGB) study [33] has attempted to address these issues by comparing three treatment schedules of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) in the adjuvant treatment of breast cancer. Arm I gave the same cumulative total dose of chemotherapy as the standard treatment arm (arm II; DII=1.0), but over 4 months instead of 6 months (DII = 1.3). Arm III gave a total cumulative dose that was half that of the other two arms in the standard treatment period of 6 months (DII = 0.5). The results obtained in arm I were superior to those obtained in arm III as predicted from a proportional dose-response relationship. However, as yet there is no difference in outcome between arms II and III. Whether the small (2/6 = 33%) dose-density increment achieved will be sufficient to produce a clinically detectable difference in long-term results requires further follow-up.

Hematopoietic growth factors and dose-intensive treatment

The use of hematopoietic growth factors [e.g., granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)] has been shown to be generally associated with improvement of WBC nadirs and more rapid hematological recovery following chemotherapy. The use of these substances has resulted in less treatment delay as well as fewer treatment modifications due to more rapid hematological recovery. Whether the reduction in treatment-related hematopoietic toxicity will result in either a higher response rate or more durable responses remains to be seen. Using hematopoietic growth factors, with no other rescue procedure, an increase in dose intensity of 50–75% can probably be achieved. However, dose-escalation studies using dose increments of this magnitude (with or without the use of hematopoietic growth factors) assess only a small part of the range of the potential dose-response curve, the shape and nature of which remain to be determined.

High-dose chemotherapy

Dose increments on the order of 50–75% are insufficient to answer the question of the role of HDC in breast cancer.

Table 1 Ablative and subablative HDC regimens used in the treatment of breast cancer

Drugs	Schedule	Total dose range
Ablative HDC regimens[a]:		
Cyclophosphamide (C)	Divided, 3–4 days	5.6–7.5 g/m^2
Cisplatin (P)	Divided, 3–4 days	165–180 mg/m^2
Carmustine (B)	Single dose	450–600 mg/m^2
Thiotepa (T)	Single or divided dose, 3–4 days	500–800 mg/m^2
Carboplatin (Cb)	Single or divided dose, 3–4 days	800–1200 mg/m^2
Subablative HDC regimens[b]:		
C	1.5–1.75 g/m^2 per day ×3	4.5–5.25 g/m^2
VP16 (E)	12–200 mg/m^2 per day ×3	750–1200 mg/m^2
P	40–60 mg/m^2 per day ×3	120–150 mg/m^2

[a] Ablative HDC combination regimens include CBP, CT±B, and CTCb
[b] Subablative HDC combination regimens include CEP

Table 2 HDC as consolidation treatment for chemotherapy-responsive metastatic breast cancer (*ER* Estrogen receptor, *NED* no evidence of disease, *DFS* disease-free survival, *OS* overall survival)

Patients' characteristics prior to therapy:

Number of patients	Percentage of study population			
	ER-negative	Visceral metastases	CR/NED at HDC	Reference
39	46	63	38	[18]
24	43	77	33	[19]
45	63	36	24	[32]
29	48	45	34	[1]
58	45	66	34	[10]
42	66	53	25	[20]

Efficacy of HDC therapy:

Treatment-related mortality (%)	PR→CR conversion (%)	Median time to treatment failure (months)	Median survival time (months)	DFS at 2 years (%)	OS at 2 years (%)	Reference
20	36	18	NA	26	–	[18]
NA	19	13	22	18	50	[19]
22	46	7.5	NA	18	35	[32]
3	20	8	NA	25	6	[1]
9	39	9	21	18	40	[10]
6	26	8	21	17	40	[20]

One problem in this regard is the lack of an adequate definition of what constitutes true HDC. Two possible definitions exist. The first relates to hematological toxicity, with HDC being arbitrarily defined as treatment that results in hematological suppression (e.g., neutrophils $<1.0\times10^9$/l) persisting for ≥3 weeks in the absence of hematological supportive procedures (e.g., bone marrow or peripheral blood stem-cell transplantation). The other definition would be to consider doses ≥2- to 3-fold those given in conventional-dose regimens to be high doses.

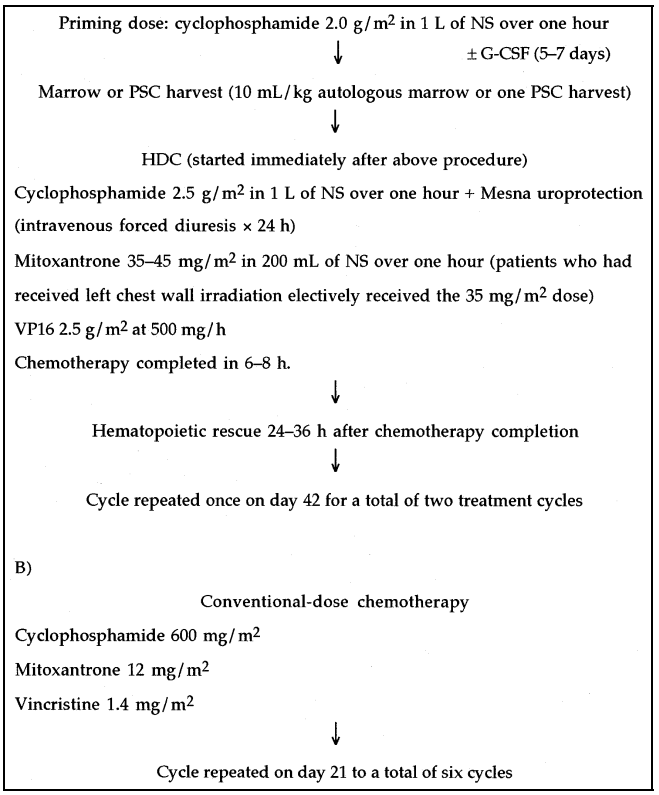

Fig. 3 **A** High-dose CNVp and **B** conventional-dose CNV treatment schedules

Neither definition is completely satisfactory since the first assumes a necessary relationship (not proven) between hematological toxicity and cytotoxicity against the tumor under consideration, whereas the second presupposes the log cell-kill response seen for exponentially growing tumors as discussed above. The definition becomes even more complex when multiagent HDC regimens are considered.

While a satisfactory definition of what constitutes HDC cannot be given, the factors to be taken into account should probably include the use of a regimen which at conventional doses is at least as effective as any other currently used treatment regimen and can be used at doses ≥3-fold those used in conventional treatment programs. Such doses would usually result in profound and prolonged hematological suppression in the absence of hematological support procedures.

A number of the HDC regimens used in conjunction with hematopoietic rescue procedures, as compared to other dose-intensive therapies that can be given without such rescue, are shown in Table 1. Few of the described regimens are satisfactory as HDC according to the previously described criteria. Frequently the regimen described has either not been tested adequately at conventional dose levels, the combination would not be regarded as consisting of the most effective first-line drugs for the treatment of breast cancer, or the difference in dose intensity between the so-called ablative and non-ablative regimens is not substantial, suggesting that effective, true high-dose regi-

Table 3 High-dose CNVp in metastatic breast cancer: patients' characteristics[a]

Characteristic	High-dose CNVp	Conventional-dose CNV
Age (years)	37.3 ± 3.4	38.1 ± 4.1
Number of patients	45	45
Performance status:		
0 or 1	39 (87)	39 (87)
2	6 (13)	6 (13)
Premenopausal/postmenopausal	34/11 (76/24)	32/13 (71/29)
Estrogen receptor status:		
Positive	12 (27)	17 (38)
Negative	24 (53)	16 (35)
Unknown	9 (20)	26 (58)
Relapsed after primary treatment	29 (64)	30 (67)
Prior adjuvant chemotherapy	25 (56)	26 (58)
Presented with stage IV disease	16 (36)	15 (33)
Visceral and locoregional disease	43 (96)	42 (93)
Locoregional disease[b]	2 (4)	3 (7)
Median disease-free interval in months (range)[c]	17 (6–23)	19 (7–41)

[a] Unless otherwise indicated, numbers in parentheses represent percentages

[b] Locoregional disease was rapidly developing inflammatory breast cancer

[c] Disease-free interval for patients with localized disease

Table 4 Projected and actual dose intensities achieved in a randomized trial of high-dose CNVp versus CNV as first-line therapy for metastatic breast-cancer

	High-dose CNVp		Conventional-dose CNV	
	Projected	Actual (%)	Projected	Actual (%)
Number of treatment cycles	2	1.8[a]	6	5.5[c]
Cycle duration (weeks)	8	11 (mean)	18	20 (mean)
		Dose/m² per week (%)		
Cyclophosphamide (g)	0.9	0.65 (90.2)	0.2	0.17 (85)
Mitoxantrone[c] (mg)	11.25	6.8 (58)	4	3.1 (77.5)
VP16 (g)	0.625	0.4 (65)	–	–
Vincristine (mg)	–	–	0.46	0.38 (82.6)

[a] Nine patients received only one cycle of high-dose CNV [five refused the second cycle and four were not given further treatment due to a prolonged (>42 days) time to hematologic recovery]

[b] In all, 21 patients in the conventional-dose CNV arm received fewer than 6 treatment cycles (2 patients received 2; 6 patients, 3; 7 patients, 4; and 6 patients, 5 cycles) due to early disease progression in 17 cases and to refusal in 4 cases

[c] Projected dose intensity calculated on the basis of 45 mg/m²

mens need to be developed. The problem is partially due to the limited number of drugs that can be given at extremely high doses. Toxicities other than hematopoietic toxicity become dose-limiting when the marrow-suppressive effects are circumvented. For example, the cardiac toxicity of the anthracyclines makes these otherwise highly effective drugs unsuitable for use in true HDC regimens.

The other problem in assessing the effectiveness of HDC is that most studies thus far conducted have been nonrandomized and used HDC as a consolidation treatment in patients who have responded to conventional-dose treatment (Table 2). When given in this fashion, HDC for patients with metastatic breast cancer has resulted in a significant (20–40%) rate of conversion from a clinical partial response (PR) to a CR, with approximately 18–25% of patients being free of disease for ≥2 years. Proponents of HDC argue that for the patient population treated, such results are significantly better than would have been expected. Those who are not convinced argue that this is a selected population by virtue of being chemotherapy-sensitive. Moreover, due to the nature of the procedure and the demands of the treatment program, patients entered into high-dose treatment protocols are usually younger and fitter than the average patient with metastatic breast cancer. This debate can ultimately be resolved only by adequately designed randomized clinical trials.

Only two randomized clinical trials comparing conventional chemotherapy and HDC for metastatic breast cancer have been reported. The first was the study of Bezwoda and co-workers [5] in which high-dose cyclophosphamide, mitoxantrone, and etoposide (VP16; HD-CNVp) was compared to conventional doses of a similar chemotherapeutic regimen consisting of cyclophosphamide, mitoxantrone, and vincristine (CNV; Fig. 3) as first-line treatment for metastatic breast cancer with the aim of achieving a CR rate of >50% in the HDC arm. The rationale for this study included evidence that the conventional-dose CNV regimen is as effective as any other combination for the treatment of metastatic breast cancer [3] and that at least two of the components (cyclophosphamide and mitoxantrone) can be given at doses in the HDC range.

Whereas the third component of HD-CNVp, VP16, has generally been found not to be effective at conventional doses in breast cancer, it should be noted that this drug is a component of many HDC regimens and that it has previously been shown to be effective at high doses in patients with breast cancer refractory to other chemotherapeutic drugs [4]. Details of the drug administration schedule are shown in Fig. 3.

In this study, eligibility criteria included an age of <50 years, histological or cytological proof of recurrent/metastatic breast cancer, and normal cardiac and renal function. A total of 90 patients (45 in each treatment arm; planned on the basis of an expected CR rate of ±20% in the conventional-dose arm) were randomized and all were eligible and assessable; this number allowed the detection of a 30% difference in the CR rate. Patients included in the study had a mean age of 37.3 ± 3.4 years in the conventional-dose arm and 38.1 ± 4.1 years in the high-dose treatment arm. The mean number of metastatic sites was 1.8 per patient, with 73% of patients having visceral metastases. Other prognostic factors were equally balanced between the two treatment arms; further characteristics of the patients are shown in Table 3. The projected and actual dose intensities achieved are shown in Table 4.

When the results were analyzed the response rate, in particular the CR rate, was significantly higher in the high-dose arm than in the conventional-dose treatment arm (Table 5), with a significant improvement in disease-free (Fig. 5) and overall survival (Fig. 6) being noted for

Table 5 High-dose CNVp versus conventional-dose CNV as first-line therapy for metastatic breast cancer: response to therapy (*PD* progressive disease)

	High-dose CNVp	Conventional-dose CNV	*P*
CR:			
First cycle	13/45 (28%)	0/45 (0)	<0.0001
≤ 2 metastatic sites	23/23 (100%)	2/26 (5%)	<0.01
Total CR	23/45 (51%)	2/45 (4%)	<0.001
PR	20/45 (44%)	22/45 (49%)	<0.01
PD	2/45 (4%)	21/45 (47%)	

patients receiving high-dose treatment. This study thus showed a clear benefit of HDC. The achievement of CRs in the high-dose arm was also clearly the factor associated with prolonged survival. Multivariate analysis (Table 6) showed that although pretreatment patient determinants had some prognostic influence, these effects were abrogated once the treatment schedule has been entered into the multivariate analysis. Furthermore, the patients who were alive and in remission for ≥ 3 years were those who had achieved a CR with the first cycle and who subsequently received a second cycle of HDC according to the protocol. These findings seem to provide further evidence for the contention that more than one treatment cycle is required for better treatment results, although the optimal number of cycles has not been determined.

This study has subsequently been criticized on a number of points. These include a lower than expected CR rate for the conventional-dose treatment arm, a relatively short duration of survival of patients in the conventional treatment arm, and the use of tamoxifen as maintenance treatment for responding patients. Although possible confounding effects of tamoxifen use cannot be negated at this point, the other issues can be addressed.

Although the CR rate of 4% found in the conventional-dose CNV arm was lower than the rate of 23% previously reported for this combination, it should be pointed out that the patient population in both arms of the randomized study consisted of women with aggressive visceral disease. Approximately one-third of the patients presented with stage IV disease; the median survival of such patients has previously been shown to be less than 1 year [9]. The median

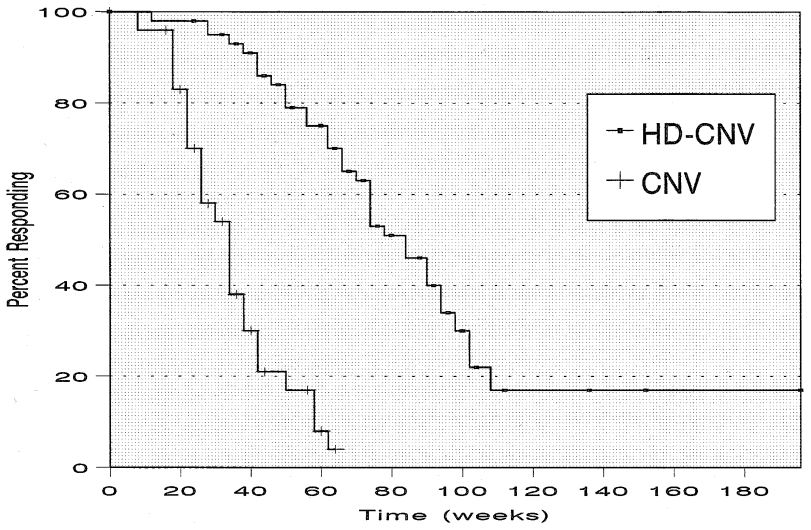

Fig. 4 Duration of response to treatment with high-dose CNVp (■) and conventional-dose CNV (+) in metastatic breast cancer

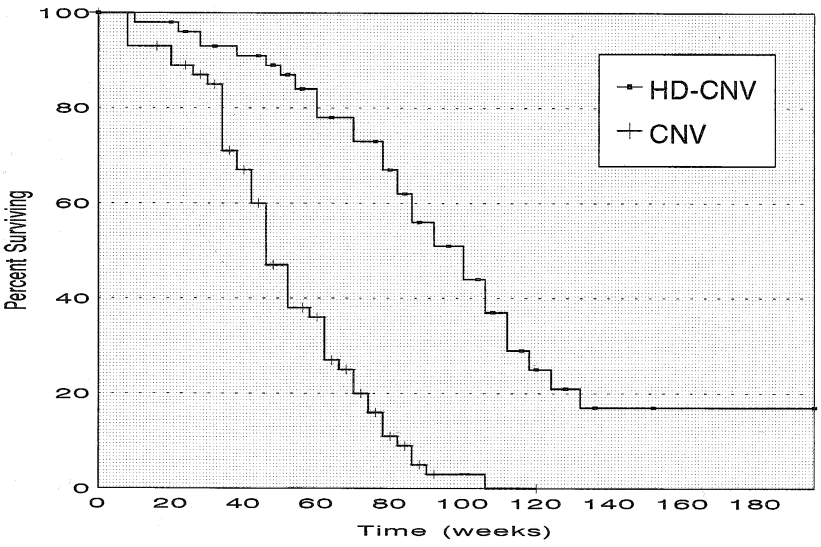

Fig. 5 Duration of survival after treatment with high-dose CNVp (■) and conventional-dose CNV (+) in metastatic breast cancer

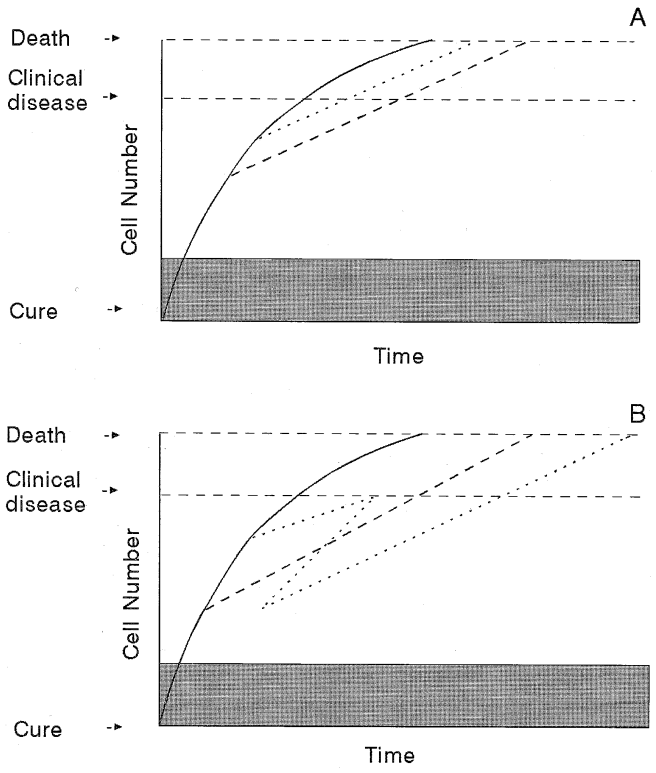

Fig. 6 Postulated kinetics of tumor regression and regrowth following **A**) first-line and **B**) delayed HDC for metastatic breast cancer (—— Tumor growth, ---- conventional therapy after HDC, – – – – cytoreduction after HDC, ▨ long-term remission

time from initial diagnosis to clinical metastatic disease for the remainder, all of whom had received adjuvant chemotherapy, was <20 months (Table 3), another indicator of aggressive disease.

The other randomized study is that of Peters et al. [27]. In this study, only patients who achieved a CR following a limited number of chemotherapy cycles (two to four) with a doxorubicin, 5-fluorouracil, and methotrexate regimen (AFM) were randomized to receive either immediate HDC or observation, with HDC being given as salvage treatment on disease progression. The results showed a significantly longer disease-free interval for patients receiving immediate HDC but shorter overall survival for this group as compared to patients in the delayed-HDC arm.

These results are difficult to interpret. Although the design is based on the classic concept of cytoreduction followed by dose intensification, only 98 patients of the total of 423 who were treated with the mitogenic chemotherapy regimen achieved a CR and were randomized to receive either immediate or delayed HDC. It must be assumed that patients who achieved a CR represent a particularly chemotherapy-sensitive population. Since no further treatment was given until disease progression in the delayed-chemotherapy arm, it would appear unlikely that significant cellular drug resistance had been induced. HDC as salvage therapy appears to have been highly effective at that point. Probably the best explanation for both results is to be found in a consideration of tumor kinetics. Perturbation of the tumor mass and growth curve may well be associated with a growth spurt approximating exponential growth. Since it would not be unreasonable to assume a lower total tumor burden for the patients in this study, the kinetic effects may have been somewhat along the lines depicted in Fig. 6.

Table 6 High-dose CNVp versus conventional-dose CNV as first-line therapy for metastatic breast cancer: multivariate analysis of prognostic factors (*NS* Not significant)

Factor	Relative risk	*P*
Number of disease sites	1.7	<0.01
Race	1.4	<0.05
Receptor status	1.2	$>0.05<0.1$
Prior adjuvant chemotherapy	0.98	NS
Chemotherapy regimen	2.1	<0.01
Number of disease sites	1.04	NS
Receptor status	0.99	NS
Race	1.03	NS

Table 7 Potential impact of new strategies together with HDC in breast cancer

Strategy	Effect on DFS at >3 years
Graft engineering	$>\pm5\%$
Decreased cycle interval (DII $>50\%$)	$>\pm12.5\%$
New drugs (CR $\pm50\%$)	$\pm12.5\%$
Immunotherapy	?

Both of the studies described above support the greater effectiveness of HDC as compared to conventional-dose chemotherapy. However, the different outcomes do not prove superiority for the induction chemotherapy approach, which probably merely reflects the disease bulk at the time of treatment.

Although the impact of dose-intensive chemotherapy has definitely been established, a number of issues related to ways of improving the results remain. A theoretical justification for the use of the induction chemotherapy approach is the question of minimizing contamination by tumor cells of blood or marrow used for hematopoietic rescue. Although G-CSF-stimulated peripheral stem cells (PSCs) probably provide the most effective means of hematopoietic reconstitution [13], the hope that these products would be less subject to tumor cell contamination has proved to be unfounded. A recent study by Mariani and colleagues [21] has shown that while peripheral blood contamination by tumor cells is less frequent than the finding of such cells in bone marrow, tumor cells are mobilized in a substantial proportion of patients following growth factor administration. Moreover, the rate of tumor cell contamination following three cycles of 5-fluorouracil, 4′ epiadriamycin, and cyclophosphamide (FEC) for high-risk stage II (without overt metastatic disease) patients was as high as 50% in bone marrow and 27% in mobilized PSCs. These findings suggest that even in patients with a low tumor burden, conventional-dose chemotherapy is probably incapable of eradicating contaminating tumor cells and that other strategies will have to be followed to reduce this and other potential sources of relapse. Although

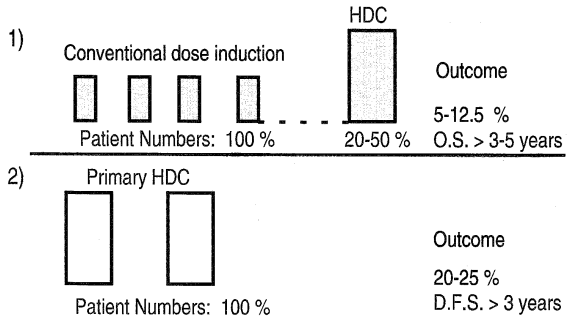

Fig. 7 Initial versus delayed HDC in breast cancer. Potential effect of treatment on long-term survival

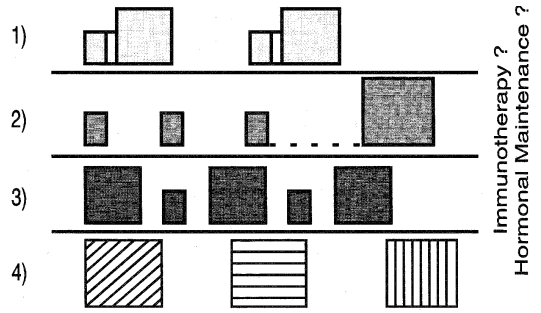

Fig. 8 Future strategies for HDC studies in breast cancer. (*1* HDC plus new effective regimens, *2* conventional-dose induction therapy followed by HDC consolidation, *3* HDC alternating with new effective drugs, *4* alternating HDC schedules)

studies need to be done, we can probably begin to estimate the potential of new technologies for minimizing tumor cell contamination (Table 7) and eradicating microscopic residual disease.

Finally, the question arises of what is to be done for patients who do not have highly chemotherapy-sensitive disease if the Peters strategy is followed (Fig. 7). The object should be to develop treatment strategies that result in optimal cytoreduction compatible with cure for the greatest number of patients. In the study reported by Peters et al. [27] the actuarial survival rate was 25% at 5 years for patients who achieved a CR, whereas in the study by Bezwoda et al. [5] the observed rate of survival of patients who achieved a CR was 40% at 3 years.

Attention now needs to be focused on the design of future HDC studies, including the issue of integration of some of the new and apparently highly effective combinations, such as those including the taxanes [7, 12, 15]. Some potential strategies for the future are outlined in Fig. 8. These may include multiple cycles of HDC, the inclusion of new agents, or the use of alternating HDC cycles. The question of which of these approaches will be more effective than current approaches can be answered only by further randomized studies.

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