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Review

A critique of the eleven randomised trials of high-dose chemotherapy for breast cancer

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Abstract

Data from 11 randomised studies on high-dose chemotherapy for breast cancer are currently available. Most investigators, patients and insurers would agree that the two discredited South African trials are uninterpretable, and that the Scandinavian trial (which compares one very high-dose cycle versus six escalated dose cycles) does not ask the question of high-dose therapy versus conventional-dose therapy. Only two of the eight remaining studies randomised more than 200 patients (783 patients for the Cancer and Leukaemia Group B (CALGB) and 885 for the Dutch study). Both of these studies have trends in relapse-free survival favouring high-dose therapy. In a planned analysis of the first 284 patients entered into the Dutch study, with a median follow-up approximately 7 years, both disease-free and overall survival were significantly improved in the high-dose therapy arm. These and the other trials are discussed in detail below.

Keywords: Breast cancer; High-dose chemotherapy; Blood and marrow transplantation; Randomised trials; Metastatic; High risk

1. Introduction

In laboratory models of cancer, doses of cytotoxic chemotherapy correlate with cure, while cumulative dose correlates with longer survival for patients who are not cured [1]. Based on these observations, the optimal strategy may be high doses of chemotherapy when cure is the objective, but many repetitive smaller doses when palliation and longer survival are the goal. A strategy combining repetitive cycles of high-dose cytotoxic therapy, followed by appropriate hormonal and biological agents based on the tumour's receptors might provide both the highest cure rate and the longest survival.

The initial development of bone marrow transplant (BMT) for leukaemia, and its subsequent modification to support high-dose therapy for other malignancies, has a long and emotional history in medicine. Partly because of firmly held positions and the way large cooperative randomised trials are funded in the USA, few randomised American trials of BMT or high-dose therapy strategies have been completed. The vast majority of published randomised BMT and high-dose studies in leukaemia, lymphoma and other malignancies are European.

In contrast, two large randomised American trials of high-dose chemotherapy had actually completed accrual in breast cancer. Accrual on a third was on target until the American Society of Clinical Oncology meeting in May of 1999, where five very small or very early randomised trials were presented. These data have been over- and misinterpreted within the scientific and lay communities. The emotional level of discourse impeded dispassionate analysis of the available data, and deteriorated even further when the data from the South African adjuvant study were discovered to have been misrepresented. At ASCO in 2000, Dr Rodenhuis, presenting the large positive Dutch insurance industry randomised study, commented on the "unreasonably high expectations until 1999" and "unreasonably negative ones since 1999" for high-dose chemotherapy in breast cancer.

Contrary to commonly expressed criticism, clinical trials of high-dose therapy for breast cancer preceded expeditiously and responsibly in an orderly progression of studies and publications to randomised evaluations. The first phase II studies of combinations in untreated or responding patients with metastatic disease were published between 1988 and 1992 [2–5]. Phase II studies

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in adjuvant patients appeared in 1993 [6]. The first randomised studies were published in 1995 and 2000 [7,8].

2. Currently available randomised data

Data from 11 randomised studies are currently available. Most investigators, patients and insurers would agree that the two South African trials are uninterpretable, and that the Scandinavian trial (which compares one very high-dose cycle versus six escalated dose cycles) does not ask the question of high-dose therapy versus conventional-dose therapy (Table 1).

Only two of the eight remaining studies randomised more than 200 patients (783 patients for Cancer and Leukaemia Group B (CALGB) and 885 for the Dutch study). (Even these two studies are modest in size. In comparison, to detect the 1–2% difference favouring paclitaxel, the recent CALGB adjuvant study required approximately 3000 patients!) Both of these studies have trends in relapse-free survival favouring high-dose therapy. Since both studies were first presented early with approximately 3 years of follow-up, a substantial fraction of those currently alive and disease-free will certainly fail over time. Thus, significant differences may or may not emerge. In a planned analysis of the first 284 patients entered into the Dutch study with a median follow-up of approximately 7 years, both disease-free and overall survival were significantly improved in the high-dose therapy arm.

The Philadelphia trial is very small, with 535 patients entered, 199 randomised, 184 analysed, but only 164 received the assigned treatment. Of the 89 patients randomised to conventional therapy, at least 13 (15%) actually received BMT. Important prognostic variables were not balanced, and the comparison is compounded by a maintenance effect of up to 2 years of conventional dose chemotherapy. Planned cumulative dose in the conventional dose arm considerably exceeds that of the 'high-dose' arm. In laboratory cancer models, dose of chemotherapy correlates with curative therapy, while cumulative dose is associated with survival [1].

Of the remaining five studies, all of them with fewer than 100 patients, the very small French trial had large differences favouring high-dose therapy. The two Dukes' crossover studies clearly supported high-dose therapy. The small Dutch pilot study, considered negative by those that discounted its lack of power to detect a 30% difference, is now an object lesson is biostatistics. Disease- free and overall survival in the planned analysis of their 284 patient subset with approximately 7 years follow-up significantly favoured high-dose therapy. The even smaller MD Anderson study showed no differences, but also could not exclude a 30% difference.

Toxic mortality, 7–10% in the few studies using first-generation carmustine (BCNU)-containing regimens,

Table 1
Eleven randomised high-dose breast cancer studies

	Number randomised (*n*)	% Toxic deaths		Median follow-up (years)	% 3 year DFS			% 3 year OS			
		HDC	Control		HDC	Control	*P* value	HDC	Control	*P* value	[Ref.]
Metastatic studies											
Philadelphia Intergroup	199	1	0	3.1	6	12	0.31	32	38	0.23	[8]
Duke CR crossover studies											
Complete responders only[b]	98	NA	NA	6.3	**25**	**10**	**< 0.01**	33	38[a]	0.32	[10,11]
Bone metastases only	69	9.7	NA	4.9	**17**	**0**	**< 0.01**	28	22[a]	NA	[12]
S African (audit underway)	*90*	*0*	*0*	*6.0*	*18*	*4*	*< 0.05*	*18*	*4*	*< 0.05*	*[7]*
French PEGASE 4	61	0	0	4.4	**49**	**21**	**0.05**	55	28	0.12	[7]
Adjuvant											
Dutch phase III	885	0.9	0.2	3.5	**72**	**65**	**0.057**	84	80	0.31	[14,15]
First 284 pt subset	284	NA	NA	7.0	**77**	**62**	**0.009**	**89**	**79**	**0.039**	[14,15]
Dutch randomised phase II pilot	81	0	0	4.1	70	65	0.97	82	75	0.84	[16]
CALGB Intergroup	783	7.4	0	3.6	71	64	NS	79	79	0.29	[17]
S African (discredited)	*154*	*this study has been discredited*									*[18]*
M.D. Anderson Hospital	78	2.5	0	6.5	48	62	NS	58	77	NS	[19]
One versus six high-dose cycles Scandinavian	*525*	*0.7*	*0*	*2.0*	*68*	*62*	*NS*	*79*	*76*	*NS*	*[20]*

DFS, disease-free survival; OS, overall survival; HDC, high-dose chemotherapy; NA, not available; NS, non significant; CALGB, Cancer and Leukaemia Group B. The South African adjuvant study has been discredited and the metastatic study is being audited [9]. The Scandinavian trial does not compare high-dose therapy versus conventional-dose therapy. Thus these three studies are in italics. Significant and borderline significant differences are shown in bold. (Reprinted with permission from Antman, Reviews on Cancer Online, in press).

[a] Patients who relapsed on the conventional dose arm then received high-dose chemotherapy.

[b] Data at 6 years median follow-up.

was 0–1% in the remainder of the studies which used second- and third-generation transplant regimens. Mortality for the conventional dose arms was also 0–1%.

Thus, for metastatic studies, because of the very small numbers (no study randomised >200 patients), no firm conclusions can be drawn at all for either patients transplanted in partial or complete response. In the adjuvant setting, the two largest studies (the Dutch and American Intergroup) have significant differences in relapse rates, and survival is significantly improved in the planned analysis of the patients on the Dutch study with the longest follow-up.

3. Randomised trials in metastatic disease trials

In the Philadelphia/Intergroup study, responders after four–six cycles of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy were randomised to high-dose cyclophosphamide, thiotepa, carboplatin (CTCb) versus conventional dose chemotherapy continued until progression or for up to 24 cycles. This study, although the largest of the five metastatic disease trials, randomised only 199 patients (37% of the 535 patients entered) [8]. An additional 18% of the randomised patients were deemed ineligible or did not receive their assigned treatment leaving 164 eligible randomised patients who received their assigned treatment. Additional patients assigned to receive conventional dose therapy underwent high-dose therapy after they relapsed. No difference in disease-free, overall survival, or the percentage of patients converting from partial (PR) to complete response (CR) were observed. The PR to CR rate of 7% is strikingly low. Given the similar survival in the two arms and the less than 1% mortality rate for high-dose chemotherapy, many patients might prefer a short, intense treatment to up to 2 years of repetitive cycles of chemotherapy.

In the South African trial, 90 patients were randomised to two cycles of a high-dose anthracycline-based regimen versus conventional-dose therapy. Complete responders received tamoxifen therapy. Because of the demonstrated unreliability of the adjuvant trial by Bezwoda [9], this study is currently being audited. The complete response rate (4% versus 51%), overall response rate (53% versus 95%), disease-free survival (DFS) (34 weeks versus 80 weeks) and overall survival (45 weeks versus 90 weeks) were reported to be superior in the high-dose arm [7,10].

In two Dukes' studies with a crossover design, 453 women with metastatic breast cancer were treated with conventional-dose AFM (doxorubicin, 5-fluorouracil and methotrexate). Of 120 women who attained a CR, 98 were randomised to either immediate high-dose cyclophosphamide, BCNU and cisplatin (CBP) versus CBP at the time of relapse. 69 women with bone metastases only underwent a similar randomisation with crossover to high-dose therapy for women randomised to conventional treatment at the time of relapse. Significant differences in DFS favour the high-dose therapy in both studies. In the bone metastases study, all patients randomised to conventional therapy relapsed and then underwent high-dose therapy [11]. Although survival of the immediate BMT group in the CR study was initially reported to be shorter than for the group getting delayed BMT, with further follow-up this difference was no longer significant [12,13]. The first-generation BCNU-based high-dose regimen used in this study resulted in a 9.7% mortality.

In the French trial, 61 women with metastatic breast cancer or first relapse responding to four–six courses of conventional chemotherapy were randomised to high-dose mitoxantrone, cyclophosphamide and melphalan versus continued conventional chemotherapy [14]. The populations were well balanced for prognostic factors with the exception of pulmonary disease (15/32 in the intensive group versus 4/29 in the standard group) and central nervous system (CNS) metastasis (2 versus none). Median DFS were 20 versus 35.3 months in the standard and intensive groups ($P=0.05$). The progression rates were 79% versus 51% at 3 years and 91% versus 91% at 5 years, respectively. The median overall survivals were 20 and 43 months, with an overall survival rate of 18% versus 30% at 5 years ($P=0.12$).

3.1. Summary of randomised metastatic trials

None of these available metastatic studies randomised more than 200 patients. The two Dukes' crossover studies and the French study all have significant differences in DFS. Because of the crossover design of the Dukes' trials, survival for conventional-versus high-dose therapy can not be compared. Based on the very few patients (427 excluding the South African study) randomised to date, no firm conclusions can be drawn for patients with metastases. Furthermore, subset analyses for the even the smaller subsets of patients in either partial or complete response prior to transplant would be particularly limited due to the lack of statistical power.

Unpublished randomised high-dose therapy studies in metastatic breast cancer are shown in Table 2. Only one small study is completed and closed to accrual; the other studies do not appear to be close to their accrual goals. Thus few additional data will be available for some time.

4. Randomised adjuvant trials

The Dutch Insurance Industry funded trial with 885 randomised patients included most women eligible at

the 10 participating centres [15]. Patients received four cycles of 5-fluorouracil, epirubicin, cyclophosphamide (FEC) and then were randomised to either CTCb or an additional cycle of FEC, followed by surgery, radiation and tamoxifen for 2 years. The toxic mortality was 1 of 443 patients on standard-dose FEC and 4 of 442 on high-dose CTCb. At a median of 3 years follow-up, a trend ($P=0.057$) in DFS has emerged favouring the high-dose therapy. In a planned analysis of the first 284 patients with a median follow-up of 7 years, disease-free and overall survival were significantly improved with high-dose CTCb. The Netherlands Cancer Institute phase II pilot which had randomised 81 women with an involved apical axillary lymph node in a feasibility study of the same randomisation design had shown no differences in disease-free and overall survival with a median follow-up of 4.1 years, but could not exclude differences in survival of less than 30% [16]. In fact their study of 284 patients above had a survival difference of approximately 10%.

In the CALGB-Intergroup study, patients received CAF induction and then were randomised to high- versus intermediate-dose cyclophosphamide, BCNU and cisplatin (CBP) [17]. Although intermediate-dose CBP is not a standard regimen, the design is a pure comparison between high- and intermediate-dose CBP. As in the Dukes' crossover studies above, this first generation BCNU-based high-dose regimen resulted in a high (7.4%) mortality, which increased with patient age and significantly varied with the experience of the transplant centre. Pulmonary and hepatic toxicity were also common. With a median of 3.6 years of follow-up, significantly fewer relapses have occurred in the high-dose arm, although neither progression-free or overall survival were significantly improved. Because the study group was selected to have a tumour mortality of approximately 80% and survival is currently approximately 70% in both arms, significant differences may or may not emerge as larger numbers of relapses occur.

The South African study was reported to compare conventional CAF versus two cycles of high-dose chemotherapy with no induction conventional-dose therapy [18]. In an independent audit, discrepancies in eligibility criteria and reported data were substantial. Control group patient records were not provided for review. The title of the protocol given to the audit team suggests that the control group was treated not with CAF but rather cyclophosphamide, mitoxantrone and vincristine. Thus, the data are at best considered unreliable [9].

The small M.D. Anderson Cancer Center study randomised 78 patients to eight cycles of FAC with or without two cycles of high-dose cyclophosphamide, etoposide and cisplatin. 3 patients randomised to conventional-dose therapy underwent transplant elsewhere; 6 randomised to transplant did not receive it. With a median follow-up of 6.5 years, no advantage for high-dose chemotherapy has emerged, but the study can not exclude differences of less than 30% [19].

The Scandinavian trial compared conventional dose induction FEC followed either by one high-dose CTCb cycle versus six additional cycles of escalated doses of FEC tailored to individual tolerance (up to 1800 mg/m^2 of cyclophosphamide, 600 mg/m^2 of 5-FU, and 120 mg/m^2 of epirubicin per cycle). The planned cumulative doses for the tailored therapy exceeds doses in the BMT arm [20]. Leukaemia or myelodysplasia has developed in 8 (3%) of patients on the tailored dose arm, versus none on the BMT arm. Topoisomerase-associated leukaemias can occur early, but alkylating agent-associated leukaemias develop later than the current median follow-up of 2 years. Thus additional cases are likely. With a median follow-up of 2 years, survival is at 60% in both arms.

4.1. Summary of randomised adjuvant trials

Only three studies randomised more than 200 patients. The Scandinavian study, which compares one high-dose cycle versus six intermediate-dose cycles, does not compare conventional- versus high-dose chemotherapy. The two remaining studies each have approximately 3 years of follow-up. The largest from The Netherlands, has a trend of borderline significance favouring the high-dose arm in DFS. The US study has a significantly decreased relapse rate for the high-dose arm. To determine whether the trend in relapse rates will continue and eventually produce significant differ-

Table 2
Ongoing or unpublished randomised high-dose trials for metastatic breast cancer

Chair	Group	Accrual target	Current accrual
Piccart	Belgian Study	400	
Kanz	German GEBDIS	350	
Crump and Gluck	National Cancer Institute, Canada	300	~200
Crown	European Breast Cancer Dose Int Study	264	~50
Rosti, Marangolo and Grignani	Italy, GITMO	240	
Biron	Pegase 03	180	Closed

ences in disease-free and overall survival will require several years of further follow-up. Given that the most optimistic data project approximately a 2% DFS after the development of metastases [21], and that the median time from relapse to death is approximately 2 years, DFS provides a preliminary indication of eventual survival data.

Fortunately, data from five additional moderately large, closed randomised trials should be reported in the next year or so (Table 3).

5. What Next?

Additional follow-up of these 11 randomised trials, and the completion and presentation of the as yet unpublished randomised trials will provide a more reliable database on which to base treatment decisions in breast cancer. Certainly lessons from the randomised high-dose trials for lymphoma should caution our early interpretation of the current breast cancer randomised trials. Good risk lymphoma patients do not appear to benefit from high-dose chemotherapy. Because of early mortality, early analyses of BMT studies may favour conventional-dose therapy. Significant differences in favour of high-dose therapy may only emerge slowly. (Certainly if lymphoma studies required 4–7 years of follow-up, differences in a more indolent disease such as breast cancer may take longer.) In one French lymphoma study, conventional-dose induction therapy significantly improved disease-free and overall survival. Maintenance therapy obscures differences. We may see these patterns in breast cancer as well.

Since the initial randomised trials were planned, the taxanes have been integrated into conventional-dose therapy for metastatic disease and are being evaluated in the adjuvant setting. In the large randomised CALGB Intergroup study, adjuvant paclitaxel provides a 1–2% survival benefit [22]. In comparison, the 284 Dutch study has approximately a 15% DFS advantage and a 10% survival advantage, with a cost in terms of mortality of 1%. Thus, although the toxicity of high-dose therapy exceeds that of conventional-dose paclitaxel, the survival difference is also larger. Based on data showing a correlation of dose with response for taxanes in the laboratory [23], higher doses of paclitaxel are now under study [24–26].

Some investigators postulate a threshold dose required for effectiveness, above which survival is not improved. Because blood levels of most drugs vary approximately 2–5-fold, significant differences in serum levels are difficult to detect unless drug dosages are escalated substantially. This observation provides an alternative hypothesis to explain the outcomes of the four available studies of modestly increased chemotherapy doses without stem cell support (Table 4). In the three studies in which no differences in outcome were detected, the dose escalations were 1.13-fold in the CALGB [22] and to 1.5-fold in the two NSABP studies [27,28], probably below the level of detection. In the positive CALGB study, the dose escalation was 2-fold [29]. A 10% difference in the relapse-free survival developed by 2 years and has persisted for 10 years. The dose effect was most significant in the 20% of patients whose tumours overexpressed Her2/neu, suggesting that important therapeutic differences might be missed if biological subsets are ignored [30]. Although a threshold effect is one reasonable hypothesis to explain these data, the lack of a significant escalation in the summation dose intensity (as low as 13% in the CALGB doxorubicin escalation study) is also a reasonable and testable hypothesis.

Some have criticised the further development of high-dose therapies based on a higher priority for molecular targeted therapy. Although we all enthusiastically envision more effective, specific molecularly targeted treatments for breast cancer, few currently exist. First-generation monoclonal antibodies such as trastuzumab (Herceptin) are effective for a relatively small subset of breast cancer patients, and even for these women are not likely to be curative as single agents. Once more effective molecularly targeted therapies are developed,

Table 3
Unpublished randomised adjuvant high-dose breast cancer trials

Eligible	Chair	Group	Accrual target	Current accrual
Adjuvant trials by number of involved axillary lymph nodes (LN+)				
>9	Tallman	ECOG	550	Closed
>9	Basser	Australia, IBCSG	340	Closed
>9	Zander/Seeber	2 German studies		
>7	Roche	Pegase 01	314	Closed
>4	Russel/Nabholtz	Intl BCIRG	460	~290
>4	Bearman	Intergroup	1000	~437
>3	Leanard	UK, Anglo-Celtic	604	Closed
>3	Gianni	Milan Cancer Institute	350	Closed

ECOG, European Cooperative Oncology Group; IBCSG, The International Breast Cancer Study Group.

Table 4
Randomised adjuvant breast cancer studies of chemotherapy doses possible without stem cell support

Group (reference)	Number of cycles	Drug dose in mg/m^2			Summation dose intensity (SDI)	Ratio of highest dose density arm compared with lowest	Outcome
		Cyclophosphamide	Doxorubicin	5-FU			
NSABP B-22: 2305 patients [27]	4	600	60	–	1.0	2-fold increase in 1 of 2 drugs	No significant differences.
	2	1200	60	–	1.0		
	4	1200	60	–	1.5		
NSABP B-25: 2548 patients [28]	4	1200	60	–	1.0	2-fold increase in 1 of 2 drugs	No significant differences.
	2	2400	60	–	1.0		
	4	2400	60	–	1.5		
CALGB 3170 patients [22]	4	600	60	–	1.0	1.5-fold increase in 1 of 2 drugs	No significant differences.
	4	600	75	–	1.13		
	4	600	90	–	1.25		
CALGB 1572 patients [29]	4	300	30	300	1.0	2-fold increase in each of 3 drugs	Significantly improved DFS and survival for arm 2 and 3 over arm 1.
	6	400	40	400	2.0		
	4	600	60	600	2.0		

NSABP, National Surgical Adjuvant Breast and Bowel Project; 5-FU, 5-fluorouracil; CALGB, Cancer and Leukaemia Group B; DFS, disease-free survival.

their evaluation would still generally take several years. Most new treatments do not replace standard therapy, but are added or integrated into them. Trastuzumab and other biologically based treatments can easily be incorporated into high-dose regimens, should they prove more effective than conventional-dose therapy.

Insuring the return of uncontaminated haematopoietic stem cells may prove necessary for improving outcome. Stem cell transplants selected to deplete contaminating breast cancer cells are already underway. Enormous technological developments related to haematopoietic stem cell support (including the recombinant haematopoietic growth factors) have already improved our methods of harvesting stem cells, our understanding of the immune system and provided tools to therapeutically modulate the immune response. In addition to facilitating the evaluation of dose-intensive therapy, evolving technology has facilitated the development of cytokine therapy, recombinant vaccines and gene therapy. Stem cell transplant technology is already used to deliver new biologically based therapies, and may be required for gene or immunotherapies.

Sequential high-dose therapies, regimens incorporating new agents and studies of cell therapies or vaccines using dendritic cells are currently under study.

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