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Minireview

Randomized trials of high dose chemotherapy for breast cancer

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Abstract

‘Now is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning’
Winston Churchill in a speech to the Canadian Senate and House of Commons, December 30, 1941

In laboratory models of cancer, dose of cytotoxic chemotherapy correlates with curative therapy, while cumulative dose is associated with longer survival for those who are not cured [1]. These observations suggests a strategy of using high doses when cure is the objective but smaller doses over a prolonged period when palliation and survival are the goal. A strategy combining repetitive cycles of higher doses of cytotoxic therapy, followed by the optimal combination of hormonal and biological agents based on the tumor’s receptors might contribute to both the highest possible cure rate and the longest survival.

The development of bone marrow transplant (BMT) for leukemias, and its subsequent modification for support after high dose therapy for other malignancies, has a long, complex and emotional history in medicine. At least partly because of firmly held opinions and the way large randomized trials are funded in the United States, few American randomized trials of BMT or high dose therapy strategies have been completed. The vast majority of published randomized BMT and high dose studies are European.

Interestingly, in contrast, two large American randomized trials of high dose chemotherapy for breast cancer had actually completed accrual. Accrual on a third was on target until the presentation of five very small or very early randomized trials at the American Society of Clinical Oncology meeting in May of 1999. Results from some of these trials, which were analyzed after a relatively brief follow-up, are too premature to allow definitive conclusions. Nevertheless, these data have been over and misinterpreted within the scientific and lay communities. The remaining studies included a limited number of patients, thus restricting the statistical power of the observations.

The desire for quick answers impeded dispassionate analysis of the available data. The opportunity for collegial review of the data further deteriorated with another round of press coverage when the data from the South African adjuvant study were found to be unreliable. Rather than increasing commitment to accrual on randomized and appropriate pilot trials, accrual to the only large American study in existence at that time tricked to a halt.

In response to press coverage, Susan Edmonds from the Fred Hutchinson Cancer Research Center observed that ‘the NYT article tends to cast shadows generally on the therapy and those providing the therapy rather than pointing out early in the article (where the public will readily see it) that there are a number of very credible research institutions conducting research directed at breast cancer, some looking at high dose chemotherapy and stem cell transplantation.’ Dr. Rodenhuis, presenting the large positive Dutch Randomized study (funded by the Dutch insurance industry) at ASCO in 2000, commented on the ‘unreasonably high expectations until 1999’ and ‘unreasonably negative [opinion-ed] since 1999’ for high dose adjuvant chemotherapy for breast cancer. © 2001 Elsevier Science B.V. All rights reserved.

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1. Currently available randomized data

Data from 11 randomized studies are currently available. Full reports of four are published in journals, and seven are available only in abstract form. Although most of the studies compare one course of conventional dose therapy with one high dose cycle, the Philadelphia study and the Scandinavian studies compare one high dose cycle vs. up to 24 conventional dose cycles and six escalated dose cycles respectively. Although mortality from the high dose therapy itself was 7–10% in the few studies using first generation BCNU containing regimens, the toxic death rate was in the 0–1% range for the remainder

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

If we examine the 11 randomized trials available to date, most investigators, patients and insurers would agree that the two South African trials are uninterpretable, and that the Scandinavian trial does not ask the question of high dose therapy vs. conventional dose therapy (Table 1).

Only two of the eight remaining studies randomized more than 200 patients (783 patients for the Cancer and Leukemia Group B (CALGB) and 885 for the Dutch study). Both have trends in relapse free survival favoring high dose therapy. Since both stud-

Table 1
Eleven randomized high dose breast cancer studies

	Number randomized	Toxic deaths (%)		Median years Follow-up	3 year EFS (%)		P value	3 year S (%)		P value	Reference
		HDC	Control		HDC	Control		HDC	Control		
Metastatic studies											
Philadelphia Intergroup	184	1	0	3.1	6	12	0.31	32	38	0.23	[3]
Duke CR crossover studies											
Complete responders only	98	NA	NA	6.3	25^b	10^b	< 0.01	33	38 ^a	0.32	[4,5]
Bone mets only	69	9.7	NA	4.9	17	0	< 0.01	28	22 ^a	NA	[6]
<i>S. African (audit underway)</i>	<i>90</i>	<i>0</i>	<i>0</i>	<i>6.0</i>	<i>18</i>	<i>4</i>	<i>< 0.05</i>	<i>18</i>	<i>4</i>	<i>< 0.05</i>	<i>[7,16]</i>
French PEGASE 4	61	0	0	4.4	49	21	0.05	55	28	0.12	[8]
Adjuvant phase 3:											
Dutch phase 3	885	0.9	0.2	3.5	72	65	0.057	NA	NA	0.31	[9,10]
First 284 patient subset	284	NA	NA	7.0	77	62	0.009	89	79	0.039	[9,10]
Dutch pilot	81	0	0	4.1	70	65	0.97	82	75	0.84	[11]
CALGB Intergroup	783	7.4	0	3.6	71	64	NS	79	79	0.29	[12]
<i>S. African</i>	<i>154</i>	<i>this study has been discredited</i>									
MD Anderson Hospital	78	2.5	0	6.5	48	62	NS	58	77	NS	[14]
One vs. six high dose cycles											
Scandinavian	525	0.7	0	2.0	68	62	NS	79	76	NS	[15]

The South African adjuvant study has been discredited and the metastatic study is being audited [2]. The Scandinavian trial does not compare high dose therapy vs. conventional dose therapy. Thus these three studies are italic. Significance differences are shown in bold.

EFS: Event free survival, HDC: high dose chemotherapy, NA: not available; NS: not significant.

^aPatients who relapsed on the conventional dose arm then received high dose chemotherapy.

^bData at 6 years median follow-up.

ies were first presented at about 3 years of follow-up, significant differences may or may not emerge. In a planned analysis of the first 284 patients accrued onto the Dutch study with a median follow-up 6 years, both disease free and overall survival were significantly improved in the high dose therapy arm. (Even these studies are modest in size. In comparison, to detect the 1–2% difference favoring paclitaxel, the recent CALGB adjuvant study required about 3000 patients!)

The Philadelphia trial is small, with 535 patients entered, 199 randomized, 184 analyzed and only 164 receiving the assigned treatment. Important prognostic variables are not balanced, and the comparison is compounded by a maintenance effect of up to 2 years of conventional dose chemotherapy. 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 with fewer than 100 patients, the two Duke crossover studies clearly support high dose therapy, and the small French trial reveals large differences favoring high dose therapy. The Dutch pilot study, widely heralded as a negative study by those that discounted its lack of power to detect a 30% difference, is now an object lesson in biostatistics. Disease free and overall survival in the planned analysis of their 285 patient subset with about 6 years follow-up significantly favored high dose therapy.

Thus, because of the small size of the metastatic studies (none >200 patients randomized), no firm conclusions can be drawn, either for PRs or CRs because of the very small numbers. In the adjuvant setting, the two largest studies (Dutch and American Intergroup) show significant differences in relapse rates, and survival is significantly improved in the planned analysis of the patients with the longest follow-up on the Dutch study.

2. Randomized trials of high dose chemotherapy for metastatic disease

In the **Philadelphia/Intergroup study**, all patients received 4–6 cycles of CAF or CMF chemotherapy. Responders were randomized to high dose CTCb versus conventional dose chemotherapy continued

until progression or for up to 24 cycles. This study, the largest of the five metastatic disease trials, randomized 199 patients (36% of the 535 patients entered) [3]. An additional 18% of the randomized patients were deemed ineligible or did not receive their assigned treatment leaving 164 eligible randomized patients who received their assigned treatment. Additional patients assigned to receive conventional dose therapy underwent high dose therapy after they relapsed. The results show no difference in disease free, overall survival, or the percentage of patients converting from partial to complete response. Thus, a single cycle of high dose chemotherapy was not superior to up to 2 years of repetitive standard dose chemotherapy. Given the less than 1% mortality rate and similar survival in the two arms, many patients might prefer a short, intense treatment to repetitive cycles of chemotherapy.

In the **French trial** 61 patients with metastatic breast cancer or first relapse responding to 4–6 courses of conventional chemotherapy were randomized to 45 mg/m² mitoxantrone, 120 mg/kg cyclophosphamide, and 140 mg/m² melphalan vs. continued conventional chemotherapy [8]. The populations were well balanced for prognostic factors excepted for pulmonary (15/32 in the intensive group vs. 4/29 in the standard group) and CNS metastasis (2 vs. none). At randomization, 13 patients (21%) had responded completely. Median event free survivals were 20 and 35.3 months in the standard and intensive groups ($P=0.05$). The progression rates were 79% vs. 51% at 3 years and 91% vs. 91% at 5 years respectively. The median overall survivals were 20 and 43 months, with an overall survival rate of 18% vs. 30% at 5 years ($P=0.12$).

At **Duke**, 453 patients with metastatic breast cancer were treated with standard-dose AFM (doxorubicin, fluorouracil and methotrexate). Of 120 women who attained a CR, 98 were randomized between high dose cyclophosphamide, BCNU and cisplatin immediately vs. at the time of any relapse. Disease free survival was significantly improved for the group randomized to BMT vs. conventional therapy. Although survival of the immediate BMT group was initially reported as shorter than for the group getting delayed BMT, with further follow-up this difference is no longer significant [4,5]. Patients with bone metastases only underwent a similar random-

ization with crossover to high dose therapy, if patients randomized to conventional treatment relapsed. Significant differences in disease free survival favored high dose therapy. In fact all patients randomized to conventional therapy relapsed and then underwent high dose therapy [6].

2.1. Summary of randomized metastatic trials

Because of the small size of all of the randomized metastatic studies (all with fewer than 200 patients randomized), no firm conclusions can be drawn at all, regarding either patients in partial or complete response. The two Duke crossover studies and the French study all have significant differences in disease free survival. Because of the crossover design of the Duke trials, survival for conventional vs. high dose therapy cannot be compared.

On-going or unpublished randomized high dose therapy studies in breast cancer are shown in Table 2. Only one small study is closed to accrual and the other studies do not appear to be close to their accrual goals.

3. Randomized adjuvant trials

The **Dutch trial**, is the largest of all published studies (885 patients randomized), therefore has the greatest statistical power to detect modest differences [9]. Funded by the Dutch insurance industry, this study included most women eligible at the 10 participating centers. Patients received four cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide) and then were randomized to either an additional cycle of FEC or to CTCb (cyclophosphamide, thiotepa, carboplatin) followed by surgery, radiation and tamoxifen for 2 years. In the study as a whole, the

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 ($P=0.057$) has emerged in DFS favoring high dose therapy. In a planned analysis of the first 284 patients with a median follow-up of 6 years, disease free and overall survival were significantly better for the high dose therapy.

The **Netherlands Cancer Institute** pilot feasibility study randomized 81 women with an involved axillary lymph node after four initial courses of FEC (5-fluorouracil, epirubicin, cyclophosphamide) to either an additional cycle of FEC or to CTCb with stem cell support followed by surgery, radiation and tamoxifen for 2 years. At a median follow-up of 49 months, disease free and overall survival were similar. With the small number of patients, the randomized phase II pilot study could not exclude differences in survival of less than 30% [11], and in fact their 284 patient study above has a survival difference of about 10%.

In the **CALGB/Intergroup study** patients received a CAF (cyclophosphamide, adriamycin, 5-fluorouracil) induction then were randomized to high vs. intermediate dose cyclophosphamide, BCNU, cisplatin (CBP) [12]. Scientifically, this design is a pure comparison between high and intermediate dose CBP, although some have objected that intermediate dose CBP is not a standard regimen. This first generation BCNU-based high dose regimen resulted in a 7.4% mortality, which significantly varied with the experience of the transplant center and increased with patient age. Pulmonary and hepatic toxicity was substantial. With a median of 3.6 years of follow-up, differences were not significant in either PFS or OS between the two groups. Significantly, fewer relapses have occurred in the high dose arm. The study group was selected to have a tumor mortality of $\sim 80\%$. Survival, currently around 70% in both arms, will

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

Chair	Group	Accrual target	Current accrual
Crown	Eur Brst Ca Dose Int Study	264	at ~ 50
Biron	Pegase 03	180	closed
Rosti, Marangolo, and Grignani	Italy, GITMO	240	
Piccart	Belgian study	400	
Crump and Gluck	NCI Canada	300	at ~ 200
Kanz	German GEBDIS	350	

almost certainly fall with time, and significant differences may or may not emerge.

The **Scandinavian trial** compared induction of FEC followed by one high dose cycle of CTCb vs. six additional cycles of escalated doses of FEC tailored to individual tolerance (up to 1800 of cyclophosphamide, 600 of 5-fluorouracil, and 120 of epirubicin per cycle). The planned cumulative doses for tailored therapy actually exceeded that for the BMT arm. Thus this study assesses the role of one cycle of high dose therapy and six cycles of intensified chemotherapy [15].

With a follow-up of 2 years, survival is at 60% in both arms. Leukemia or myelodysplasia has developed in 3% of patients on the tailored dose arm, vs. none on the marrow transplant arm. Additional cases are likely. Topoisomerase-associated leukemias can occur early but alkylating agent-associated leukemias develop later than the current median follow-up of 2 years.

The **South African study** was reported to be a comparison of conventional CAF vs. two cycles of high dose chemotherapy with no preceding induction therapy [13]. An independent audit team reported many inconsistencies in eligibility criteria, as well as reported data. Records of treatment and outcome for the control group were not provided for review. The title of the protocol given to the audit team suggests that the control group was treated with cyclophosphamide, mitoxantrone and vincristine and not CAF. Based on these findings the abstract has been withdrawn and the data are, at best, considered unreliable [2].

The small **The MD Anderson Cancer Center** study

randomized 78 patients to eight cycles of FAC with or without two cycles of high dose chemotherapy with cyclophosphamide, etoposide and cisplatin. Three patients randomized to conventional dose therapy were transplanted elsewhere and six patients randomized to transplant did not receive it. With a median follow-up of 78 months, no advantage for high dose chemotherapy has emerged, but the study cannot exclude differences of less than 30%. [14]

3.1. Summary of randomized adjuvant trials

Only three studies randomized more than 200 patients. The Scandinavian study, which compares one high dose cycle vs. six intermediate dose cycles, did not compare conventional vs. high dose chemotherapy. The largest study, from The Netherlands, shows a trend favoring the high dose arm. The US study has a significantly decreased relapse rate for the high dose arm. Whether the trend in relapse rates will continue and eventually produce significant differences in disease free and overall survival will require several years of further follow-up. The median follow-up on the Dutch, US and Scandinavian studies is only 2–3.6 years, respectively. Given that the most optimistic data show that ~2% of patients survive disease free after the development of metastases [17] and that the median time to death after relapse is about 2 years, event free survival can provide an early indication of what survival curves will eventually show. Fortunately data from five additional closed randomized trials may be reported in the next year or so (Table 3).

Table 3
Ongoing or unpublished randomized high dose adjuvant breast cancer trials

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

Table 4
Randomized adjuvant studies of chemotherapy dose in breast cancer at conventional doses

Group, reference Number of patients	Number of cycles	Drug dose (mg/m ²)			Summation dose intensity	Ratio of highest dose density arm compared to lowest	Outcome
		Cyclophos- phamide	Doxo-rubicin	5FU			
CALGB 1572 patients [18]	4	300	30	300	1.0	2 fold increase in each of three 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		
CALGB 3170 patients [22]	4	600	60	–	1.0	1.5 fold increase of one of two drugs	No significant differences.
	4	600	75	–	1.13		
	4	600	90	–	1.25		
NSABP B-22: 2305 patients [20]	4	600	60	–	1.0	2 fold increase in one of two drugs	No significant differences.
	2	1200	60	–	1.0		
	4	1200	60	–	1.5		
NSABP B-25: 2548 patients [21]	4	1200	60	–	1.0	2 fold increase of one of two drugs	No significant differences.
	2	2400	60	–	1.0		
	4	2400	60	–	1.5		

4. Critique of conclusions drawn in the scientific and lay literature

A number of conclusions have appeared in the press and literature that bear examination:

4.1. *There is a threshold effect but no evidence for dose response based on the NSAPB and CALGB adjuvant studies at conventional dose*

The first statistically robust study of higher doses of adjuvant chemotherapy was conducted by the CALGB (Table 4). Patients with node positive breast cancer were randomized to one of three doses of CAF [18]. The high dose arm involved CAF at doses of 600, 60 and 600 mg/m² respectively and the low dose arm 300, 30 and 300 mg/m². A 10% difference in the relapse free curve developed by 2 years and has persisted through 10 years (i.e. an approximately 20% reduction in mortality). This study has been criticized in that the low dose is lower than the current standard dose, and may be below a threshold dose required for effect (i.e. within the ‘no treatment’ range). The dose effect was most prominent in the

20% of patients whose tumors overexpressed Her2/neu. For tumors without Her2/neu overexpression, no dose effect was seen [19].

However, two studies of cyclophosphamide conducted by the NSABP failed to show an effect of doubling the cyclophosphamide dose with the doxorubicin dose held constant, a 1.5 fold summation dose escalation [20,21]. Finally, a two-by-two factorial study conducted by the CALGB failed to show a dose effect for a 25 and a 50% increase in doxorubicin dose (at most a 25% summation dose escalation) [22].

In the first positive CALGB study, all three agents were increased twofold. In the second CALGB study, only doxorubicin was increased, and only 1.5 fold. Considering that the other one or two agents were administered at the same dose in all the arms of the study, the small escalation of one of the three agents was probably below the level of detection. The difference in cumulative dose intensity (CTI) was only a 1.25 fold increase. Because blood levels of most drugs vary about 2–5 fold, no significant differences can be detected in serum levels unless drug dosages are escalated substantially.

Thus while a threshold effect is one reasonable hypothesis, the lack of a significant escalation of the summation dose intensity (as low as 13% in the CALGB study of doxorubicin escalation) is also a reasonable and testable hypothesis for the lack of effect in the studies with smaller dose escalations.

4.2. *The phase II studies were positive because of patient selection*

Patient selection applies to all studies. In a comparison of the CALGB and Autologous Blood and Marrow Transplant Registry (ABMTR) databases, patients who were not candidates for high dose therapy were excluded from the CALGB database (e.g. those with marrow involvement, no response to conventional therapy and patients over age 60). Patients were removed from the ABMTR database if they were ineligible for the CALGB studies: patients who had failed any prior regimens for metastatic disease. In fact, 58% of the patients in the CALGB database were not eligible for high dose therapy, but 63% of the ABMTR patients were not eligible for the CALGB studies! [23]. The subsequent comparison of the two databases showed a significant survival advantage for high dose therapy. Certainly randomized studies are needed to sort out these kinds of bias, but selection biases occur in both directions.

4.3. *Randomized trials were inordinately delayed*

In the late 1970s and early 1980s high doses of single agents, and then combinations were evaluated in phase I studies for advanced refractory cancer (Table 5). Short responses were observed, supporting the importance of dose. Disease free survival was rare. Once toxicities were predictable, high dose studies for women with untreated or responding metastatic breast cancer began, with published reports appearing in 1988–1992 [24–27].

A phase 2 trial using a first generation high dose regimen in an adjuvant setting was published in 1993 with promising disease free survival but reported a transplant mortality of 24% [28]. Additional phase I studies of effective regimens with lower regimen-related mortality [29] were developed along with improved supportive care. The availability after 1988 of hematopoietic growth factors such as G-CSF [30] and GM-CSF [31] modestly improved time to marrow recovery in randomized trials [32,33]. The observation that stem cells could be mobilized after chemotherapy (and even more efficiently with growth factors) [34] led to substantially decreased aplasia, morbidity and costs of autotransplant using stem cells and marrow [35] and then mobilized stem cells alone [36]. Randomized metastatic and adjuvant trials were designed with results appearing in 1995 and 2000 respectively [3,7].

In this orderly progression of studies and publications (contrary to commonly expressed criticism), clinical trials of high dose therapy in breast cancer proceeded to randomized evaluations expeditiously and responsibly. In fact, designing randomized trials prior to establishing an optimal transplant regimen with an acceptably low mortality may confuse rather than facilitate evaluation of high dose therapy.

4.4. *American physicians have acted as if there was no need for randomized trials*

Americans' willingness to apply results from randomized trials is not always reflected in their willingness to participate in randomized trials. In the ABMTR data base, the number of patients treated with high dose therapy increased rapidly after the startlingly positive South African randomized study was published [7]. The rush to transplant slowed in response to the presentation of the small negative randomized Dutch and MD Anderson hospital studies presented at ASCO and published in *Lancet*, re-

Table 5
History of the development of high dose regimens for breast cancer

Year Published	Phase	Breast cancer population	Regimen	Reference
1970–88	1	advanced refractory cancer	studies of single agents, then combinations	
1988–1992	2	untreated or responding metastatic	combinations	[24–27]
1993	2	adjuvant	first generation high dose regimens with a transplant	[28]
1995 or 2000	3	metastatic	randomized trials	[3,7]

spectively, in 1998 [11,14,37] and then dropped precipitously with the presentations of the five studies and the press coverage at ASCO in 1999.

Thus, the actual use of the high dose strategy has been exquisitely data driven – based on the data available at the time the transplants were recommended, although Americans appear reluctant to participate in randomized trials.

4.5. 'We must pay for it only in controlled trials until we get answers. In particular, conducting pseudotrials that 'test' various high dose drug combinations is not justified given the current data' [38]

Despite these views expressed by Miller and Sledge [38], Cancer Center programs with an expertise in high dose therapy for breast cancer such as Duke, Hopkins, Stanford, CO, Karmanos, MD Anderson, Columbia and others have elected to continue their pilot studies to insure that high dose regimens evolve with the rest of medicine incorporating new drugs and strategies. Such pilots provide required pilot data for the next generation of clinical trials.

4.6. What constitutes 'standard' adjuvant therapy has not remained stagnant; even a positive high dose chemotherapy trial would need to be interpreted differently in the taxane era. Interest has now turned toward molecular-targeted therapy

The best data currently available suggest a 1–2% survival benefit for adjuvant paclitaxel [22]. However, the 285 Dutch study has about a 15% disease free survival 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. Furthermore pilot trials based on data showing a dose response for taxanes now are evaluating higher dose paclitaxel [39–41].

We all enthusiastically anticipate more specific and effective molecularly targeted treatments for breast cancer, However few currently exist. Once developed their evaluation will probably take several years. First generation biologically based treatments such as Herceptin are not curative in themselves, are unlikely to result in large survival differences, and are

effective against only a relatively small subset of breast cancers. For this subset of women, Herceptin and other biologically based treatments can be easily incorporated into high dose regimens.

In contrast, high dose therapy is now relatively safe and partially evaluated. If the 10–15% differences in survival and disease free survival in the analysis of the 285 patient Dutch trial with 6 year follow-up were substantiated along with the 1% mortality, some women would elect high dose treatment. Effective treatments generally become increasingly cost effective, as physicians anticipate and ameliorate toxicities. Thus high dose therapies will not remain stagnant either. Stem cell transplants selected to deplete contaminating breast cancer cells, sequential high dose therapies, regimens incorporating new agents and studies of cell therapies or vaccines using dendritic cells are already underway.

5. The “end of the beginning”. Going forward

Additional follow-up of these 11 randomized trials, and the completion and presentation of the as yet unpublished randomized trials will provide more reliable data on which to base decisions regarding high dose chemotherapy in the management of high-risk primary and metastatic breast cancer. Insuring the return of an uncontaminated marrow may prove necessary for improving outcome. Based on the enormous technological developments related to hematopoietic stem cell support, high dose chemotherapy can now be safely administered in the ambulatory setting, resulting in substantial reductions in financial cost. Recombinant hematopoietic growth factors have facilitated harvesting stem cells, improved our understanding of various aspects of the immune system, and provided tools to modulate the immune response to therapeutic benefit. In addition to facilitating the testing of dose intensive therapy, evolving technology has facilitated the development of cytokine therapy, gene therapy and recombinant vaccines. Stem cell transplant technology already is being used to deliver new biologically based therapies. Some gene or immunotherapy may require stem cell transplant technology.

Certainly lessons already learned from randomized trials of high dose therapy for intermediate and high-

grade lymphoma should at least caution our interpretation of early breast cancer randomized trials: Good risk lymphoma patients do not benefit from high dose chemotherapy. Significant differences in favor of high dose therapy may not emerge for 4–7 years. (Certainly if lymphoma studies required years of follow-up, differences in breast cancer, a more indolent disease, may take even longer to become apparent.) Because of early mortality, early analyses of studies of BMT often favored conventional dose therapy. Induction therapy significantly improved disease free and overall survival in one French lymphoma study. Trials of high dose chemotherapy vs. maintenance therapy in relapsed lymphoma are negative, while conventional dose therapy followed by a high dose treatment vs. observation or one more conventional dose treatment are positive. We may see these patterns in breast cancer as well.

Americans have completed relatively few randomized BMT trials. Virtually all randomized BMT trials in leukemia and lymphoma were completed in Europe. A mechanism for designing and completing randomized high dose trials is under consideration by the NHLBI and NCI and would significantly enhance the design and completion of high dose studies in the USA.

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