High-Dose Chemotherapy and Peripheral Blood Progenitor Cell Transplantation in the Treatment of Breast Cancer*

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Key Words. High-dose chemotherapy · Autologous transplantation · Breast cancer · Metastatic · High-risk primary · Hematopoietic stem cells

ABSTRACT

Each year in the USA, 180,000 new cases of breast cancer are diagnosed and about 44,000 women die of the disease. Current primary treatment consists of adjuvant chemotherapy and hormone therapy, and statistics show that combination chemotherapy favorably influences the outcomes in both node-negative and node-positive primary disease. However, a significant number of breast cancer patients succumb to the disease, and nearly every patient diagnosed with metastatic breast cancer will be dead within five years.

High-dose chemotherapy (HDC) and peripheral blood progenitor cell transplantation (PBPCT) are based upon laboratory and clinical observations of the ability to modify growth properties of quiescent and replicating cancer cells. A large number of HDC and PBPCT regimens have been evaluated for treatment of metastatic breast cancer, and recent autologous bone marrow transplantation data indicate that three HDC regimens (CPB, CTCb and cytoxan and thiotepa) predominate. Unfortunately, negative media coverage surrounding and subsequent to the presentation of preliminary findings reported at the May 1999 American Society of Clinical Oncologists, that were not allowed adequate follow-up time for full analysis of treatment results, has had a detrimental effect on the ability to conduct trials in this area.

Several randomized trials have been conducted in both the metastatic and high risk primary disease settings. Thorough analysis of these studies indicates an evaluable improvement in favor of HDC and PBPCT in three of the four randomized studies performed in metastatic breast cancer and two of the four high risk primary studies. Also, initial evaluations found that quality of life appeared comparable in patients receiving either HDC or not. Each randomized trial studied asks a different question and, depending on the intensity of HDC regimen, the intensity and duration of the standard dose chemotherapy control and the schedule of events in relation to induction chemotherapy, the outcomes may be quite variable. Still, certain general trends are indentifiable. HDC alone will not completely cure breast cancer and should be considered as part of an overall therapeutic plan. In some of these studies, significantly longer follow-up is required before definitive analysis can be completed. The Oncologist 2000;5:1-13

INTRODUCTION

Each year in the USA, 180,000 new cases of breast cancer are diagnosed and about 44,000 women succumb to the disease [1]. Each death, in essence, reflects a failure of primary treatment. Currently in primary disease, despite even relatively recent skepticism [2], adjuvant chemotherapy and hormonal therapy constitute standard of care, and a large statistical overview has established that combination chemotherapy favorably influences outcome in node-positive and node-negative primary disease [3]. Significant numbers of patients, however, still succumb to their disease. Progress has been limited in metastatic breast cancer, with outcomes in the last...
decade having deteriorated. This is believed to reflect widespread use of adjuvant chemotherapy in primary disease, this being a negative prognostic factor for disseminated disease [4]. The stark reality is that standard dose chemotherapy (SDC) for breast cancer is poor. Nearly every woman diagnosed with metastatic disease will be dead within five years, and over half of those with primary breast cancer succumbs to the disease despite best surgery, chemo-, radiation- and hormonal therapy. New drugs, including the taxanes and biologic therapies such as Herceptin, have done little to fundamentally change this dismal picture with improvements measured in weeks of median outcome, and little demonstration of increased frequency or duration of complete remissions (CR).

This lack of significant outcome improvement has been a driving force in the evaluation of high dose chemotherapy (HDC) and peripheral blood progenitor cell transplantation (PBPCCT). A recent update indicates that 4,503 autotransplants were performed for breast cancer in 1994 and 1995, and incomplete data for 1996 and 1997 indicate a further increase to 5,695 transplants [5]. Increasingly, this modality has been offered earlier in the natural history to deal with primary disease at high-risk for dissemination. While 7% of transplants were performed for primary disease in 1989, by 1995 this had increased to 49%. Only about 50% of PBPCCT performed in North America [6] are reported and consequently these data are an underestimate. It is disappointing to note that only 1% of the patients transplanted for stage IV disease and 11% for stage II or III disease have been entered into national randomized trials in the USA.

Widespread utilization of HDC and PBPCCT has coincided with improvement in safety such that, in experienced hands, transplant-related acute mortality is less than 5% and in certain centers approaches less than 1%. This has allowed the procedure to be performed largely as outpatient, thereby markedly reducing cost [7].

Despite much clinical research, the appropriate role for HDC remains today unresolved. A barrage of negative media reporting surrounding the 1999 American Society of Clinical Oncology (ASCO) meeting, suggested to many patients and physicians final conclusions disparaging of this therapy. Prior to and between posting of abstracts and actual presentations, investigators were prohibited from discussing data. Consequently media reports were unencumbered with critical evaluation of data and fact. In the emotional heat, reason appeared abandoned. News anchors on national television were presenting abstract data before official posting and before investigators had even seen the data. Within 24 hours of the ASCO posting of abstracts, editorials presenting policy conclusions were published in the New York Times by individuals who had never seen the data. This one-sided reporting has resulted in confusion and anxiety for patients with poor prognosis disease who are facing difficult decisions and for their doctors advising them.

### Basis for HDC and PBPCCT

Cure of patients with acute leukemia [8-10], lymphoma [11-15], testicular cancer [16-21], and ovarian cancer [22-25] by transplantation strategies is predicated on achieving a complete response. Adjuvant chemotherapy for breast cancer has established that the elimination of micrometastases is achievable, even with regimens noncurative in metastatic disease [26-30]. In metastatic disease, SDC frequently results in disease shrinkage but seldom produces a CR. The utilization of HDC and PBPCCT as a means of increasing the frequency of complete responses is consistent with the results obtained in the other diseases summarized above and could reasonably be expected to provide the necessary basis for building toward disease cure.

HDC and PBPCCT are based upon laboratory and clinical observations of the ability to modify growth properties of both quiescent as well as replicating cancer cells. These derive from seminal reports of Skipper and Schabel [31, 32] as well as Frei and others [33], defining dose, dose intensity, schedule of therapy, and the chemotherapeutic agents. Three of Skipper’s rules provide much of the scientific underpinning of HDC and PBPCCT [34].

#### Rule 1

The total tumor-cell-kill hypothesis states, “In order to achieve cure, it is necessary to eradicate the tumor cells (both T/0 and T/R cells in the primary and metastatic sites) using tolerated local and/or systemic treatment.” Clearly eradication of the total cancer cell burden is the aim. The systemic nature of metastatic and high-risk primary breast cancer mandates combining systemic and local therapy. However, the larger the cancer burden, the greater the risk of developing chemotherapy resistance. Goldie and Coldman have shown that transition from sensitive to resistant states may occur over as few as six cancer cell-doubling intervals [35]. Rule 1 requires eradication of all sensitive and resistant cancer cells for cure and therefore implies that HDC is most likely to be effective early in the disease setting and that drug combinations must address the pattern of cellular resistance.

#### Rule 2

The dose response and first order kinetics rule indicates, “There is an invariable direct relationship between the single dose of a given chemotherapy agent and the number of drug-sensitive tumor stem cells killed. In a given cancer, the same dose of a given drug will kill the same fraction or percentage (not the same number) of widely different tumor burdens of drug-sensitive cancer stem cells. It follows that in vivo dose-response curves or in vitro concentration-response curves should be (and are) exponential for homogeneous drug-sensitive tumor stem cell populations.”

This implies that at any dose, cancer burden becomes limiting. Consequently, agents with a steep dose-response curve
are most effective at the highest tolerable dose. The limitation
to dose escalation is the toxicity to the nonmalignant tissue.
PBPCT has minimized hematopoietic toxicity, and non-
hematopoietic toxicity is therefore dose-limiting such that
drugs must be selected to permit maximal escalation with
minimal and nonoverlapping nonhematopoietic toxicity.

**Rule 3**
The inverse rule reads, “There is an invariable inverse
relation between the cancer stem-cell burden and curability by
chemotherapy used alone or in the adjuvant setting.” This
implies that the greater the tumor burden, the greater the
tumor cell kill necessary for cure. Implicit is the concept that
larger cancers have greater potential for development of
drug resistance. Consequently curability of a cancer is determined
by cancer size, chemotherapy efficacy and cellular resistance
to the chemotherapy.

Understanding these rules helps define the choice of
HDC, and the optimal disease settings in which to evaluate
it become clearer.

**THE HIGH-DOSE REGIMEN**

Studies of animal and human malignancies established that
resistance to alkylating agents is rare and inversely proportional
to dose. The dose-response relationship for these agents is log-
linear and does not appear to plateau within the clinically
relevant range. The major dose-limiting toxicity of the alkylators is
myelosuppression. Other classes of agents do not uniformly
show this steep response and often exhibit nonhematologic tox-
icity close to myelosuppressive dose. HDC in breast cancer is
predicated on escalation of dose to the maximal level below
that at which nonhematopoietic toxicity manifests.

Cancer cell heterogeneity suggests that combination ther-
apy should be more effective than single agents. This is an
established principle of most curative regimens in other can-
cers. In metastatic breast cancer, the survival benefit of com-
binations has been more difficult to demonstrate [36, 37].
Agents used in HDC should be active against breast cancer at
the dose employed. Most drugs, however, have not been evalu-
ated at high dose because of myelosuppression. While TBI is
important in conditioning for transplantation for leukemias,
lymphomas, and myeloma, it is of limited value in breast can-
cer because doses required for cancer eradication often exceed
tolerable thresholds.

Alkylating agents have been the anchor for most high-
dose regimens for breast cancer. They have a high proportional
dose between the HDC and the SDC setting [38]. In vivo
and in vitro data demonstrated noncross-resistance among
selected alkylators [39]. Preclinical data established ther-
apeutic efficacy and synergy of combined alkylating agent
regimens [33, 34].

Nonhematologic toxicities of a number of alkylating agents
do not overlap. The major toxicity of cyclophosphamide is
hemorrhagic myocarditis; of platinum, nephrotoxicity, and neu-
rotoxicity; of carmustine, hepatic, and pulmonary toxicity; of
thiotepa, mucosal, and central nervous system toxicity; of busul-
fan, enterocolitis, and seizures; and of melphalan, mucositis.
It is therefore possible to select agents with nonoverlapping
toxicities for HDC and PBPCT. However, organ toxicity has
been encountered at much lower doses with certain combina-
tions of drugs and this relates in part to pharmacokinetic (PK)
and pharmacodynamic (PD) interactions [41, 42].

In summary, alkylator combinations meet most require-
ments for effective transplant regimens including efficacy
at the dose employed, steep dose-response curves without
plateau, high proportional dose, noncross-resistance and
nonoverlapping nonmyelosuppressive toxicities.

Although a large number of HDC and PBPCT regimens
have been evaluated for metastatic breast cancer, recent autol-
ogous bone marrow transplantation (ABMTR) data indicate
that three HDC regimens predominate [43]. The three most
ubiquitously utilized HDC regimens include STAMP I com-
prising cyclophosphamide, cisplatinum and carmustine (CPB)
[44]; STAMP V consisting of cyclophosphamide, thiotepa,
and carboplatinum (CTCv) [45]; and the regimen of cytoxan
and thiopeta [46]. These regimens have never been directly
compared to one another in randomized fashion. It is important
to understand that CTCv was developed as a “kinder and
gentler” alternative to CPB.

**DOSE INTENSITY IN BREAST CANCER**

This topic has remained controversial. Reviews of the
identical literature by Hryniuk and Bush [47] and Henderson,
Hayes and Gelman [48] have come to opposing conclusions.
Reviewing therapeutic outcomes of various SDC treatment
protocols, Hryniuk and Bush noted a clear dose-response rela-
tionship. Henderson and colleagues expressed caution con-
cerning the analytic methods. The subject of the dose-response
relationship was reviewed by Frei and Canellos [35], and the
results of early dose-intensive therapeutic efforts have been
reviewed by Peters [34, 49]. The consistent finding is that dose
intensification appears to have a major positive effect on
response rate and survival. A complete response is likely to
be a prerequisite for cure in this disease. The importance of
dose intensity is emphasized by two recent meta-analyses.
Hryniuk and coworkers constructed a single agent database
and showed clearly that response rates and median survival
related linearly with the summation dose intensity (SDI) of
the treatment arms with one SDI unit increment increasing the
CR plus partial remission (PR) rate by approximately 30% and
median survival by 3.75 months [50]. These quantitative
aspects of the SDI-response relationship do, however, require
prospective evaluation and do not include an evaluation of the
size of the individual dose. Fossati and colleagues, in a
large meta-analysis, showed statistically significant improve-
ment both in response rates and overall survival (OS) when
chemotherapy regimens were compared with the same regimens delivered with less intensive schedules [51].

**HDC FOR HIGH-RISK PRIMARY BREAST CANCER**

The importance of adjuvant chemotherapy in primary breast cancer with high-risk factors for progression including significant node positivity and large size of primary tumor is established. Noncurative regimens for metastatic disease have produced consistent, yet modest, improvements in disease-free survival (DFS) and OS in primary breast cancer.

Analysis of reported adjuvant SDC in primary breast cancer led Budman and colleagues [52] to suggest a dose-response relationship. Certain randomized data support this view. The Cancer and Leukemia Group B (CALGB) compared three doses and schedules of CAF (CALGB 8541) as adjuvant breast cancer treatment. “Intermediate” and “high-dose” arms produced superior DFS and OS [53, 54]. Single institution studies of sequential HDC indicate a potential advantage compared to SDC [55].

NSABP B-22, however, failed to detect differences in either DFS or OS over a fourfold intensification of cyclophosphamide [56]. A follow-up study (B-25) has been completed but the analysis only preliminarily communicated, indicating that while of modest magnitude, the highest dose of cytorexan is approaching though has not yet reached a significant level of difference. From these data it is evident that escalation of a single drug, cyclophosphamide, has limited ability to produce a significant improvement for patients with primary breast cancer.

Two initial phase II studies with sufficient patients and follow-up provided the initial impetus for the subsequent randomized studies of HDC in high-risk primary breast cancer [57, 58]. In these two studies, with median follow-up of more than two years at initial reporting, 72% and 92% of patients remained event-free. The updated data indicate median follow-up of 85 patients treated with CAF followed by high-dose CPB of 6.9 years (range 4.9 to 9.6). The event-free survival (EFS) is 62%. The OS is 68% [59]. Updated data from the second study discuss 67 patients treated with high-dose sequential cyclophosphamide, methotrexate, and melphalan with a median follow-up of 48.5 months and a lead follow-up of 78 months [60]. Actuarial relapse-free survival (RFS) is 57% and OS 70%. These results are significantly better than historical or contemporary data obtained for similar prognosis patients receiving SDC. A number of other phase II trials have also reported encouraging results in high-risk primary disease [61-64]. ABMTR reported outcomes [43] in high-risk primary disease are consistent with the phase II reports.

Preliminary analysis of three randomized investigations of HDC for high-risk primary disease involving 10 or more positive nodes was presented at the ASCO meeting 1999. Summary data of these as well as two previously reported under-powered randomized studies are presented in Table 1. Patients on CALGB 9082 had stage II or IIIA breast cancer with 10 or more involved lymph nodes without evidence of metastatic disease and with normal organ function, informed consent and prior approval of insurance coverage. Analysis was by intention to treat with the primary endpoint EFS. The original sample (340 patients) was powered to detect a 20% difference in EFS after three years of follow-up of all patients. This was doubled in 1995 because of declining treatment-related mortality (TRM) and morbidity, thereby permitting detection of a 14% difference in EFS at five years. OS was not a primary endpoint because patients on the nontransplant arm were eligible for HDC if they relapsed.

Of an initial 884 patients 785 were equally randomized to receive either HDC or intermediate dose CPB (IDC). Ninety-three and 94% received the projected therapy. Twenty patients have received HDC after recurrence on the IDC arm and five received HDC a second time after relapse.

**Table 1. Summary of randomized studies of HDC in primary disease**

<table>
<thead>
<tr>
<th>PI/study/HDC regimen</th>
<th>Patient n</th>
<th>Follow-up</th>
<th>Current results of study</th>
</tr>
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<tbody>
<tr>
<td>Peters/CALGB 9082; SWOG 9114; NCIC MA13 /CPB [65]</td>
<td>874</td>
<td>3.5 yrs</td>
<td>34% relapse reduction; EFS &amp; OS same (short follow-up); 7% TRM—center and age dependent</td>
</tr>
<tr>
<td>Bezwoda/South African/CNV [66]</td>
<td>154</td>
<td>5 yrs</td>
<td>Significant improvement in DFS and OS; no TRM</td>
</tr>
<tr>
<td>Berg/Scandanavian Study Group/CTCb [67]</td>
<td>525</td>
<td>1.7 yrs</td>
<td>133 relapses; OS same (very short follow-up); total dose on nontransplant (NT) arm higher; no TRM; 7 MDS/AML (NT arm)</td>
</tr>
<tr>
<td>Rodenhuis/Dutch Study Group/CTCb [68]</td>
<td>81</td>
<td>4.5 yrs</td>
<td>No difference in DFS or OS; small study; protocol treatment deviation</td>
</tr>
<tr>
<td>Hortobagyi/MDA/CEP [69]</td>
<td>78</td>
<td>4 yrs</td>
<td>No difference in DFS or OS; study closed because of slow accrual; protocol treatment deviation</td>
</tr>
</tbody>
</table>

OS = overall survival; DFS = disease free survival; TRM = treatment-related mortality.
on the HDC arm. The study was well balanced for all demographic parameters. With median follow-up at 42 months, EFS was not significantly different. From both prior data and the study design, this follow-up is too short for data interpretation (Fig. 1). The sample size was doubled in 1995, and consequently the first 341 patients have been followed for a minimum of three years with a medium follow-up of 5.1 years. This limited sample size reduces the statistical power but gives an indication of how the data may well mature. Analysis of the first 341 patients shows that at 36 months there is an actual difference in EFS in favor of HDC of 12%; at five years the actuarial results were 8% and at the lead follow-up 84 months they were 25%. However, due to limited sample size the \( p \) value is 0.1, not statistically significant. At this sample size, the study was powered to detect differences only in excess of 20% EFS.

EFS in the study is primarily determined by relapses and TRM. TRM occurs in the first year whereas relapse occurs over the entire study. Fewer relapses have occurred in those who have received HDC throughout the first three years of follow-up. There were 126 relapses on the IDC arm and 85 on the HDC arm. This is a reduction in relapse frequency from 32.2% (95% confidence interval [CI]; CI 27.6% to 36.9%) to 21.6% (95% CI 17.5% to 25.6%). Note that there is no overlap between the CI. This represents a 34% reduction in relapse frequency.

TRM was 7% overall with a 3% mortality in the first 100 days. Causes of TRM were infections, pulmonary toxicity, pulmonary hemorrhage, and hemolytic uremic syndrome. There was a relationship between the number of patients accrued in a given center and the TRM, with the largest accruing center at 5.9%, the second largest at 7.9% and other centers at 10%. An apparent relationship between TRM and age was suggested, with patients under 40 years at 2%, patients under 65 at 10% and over 65 at 20%. However, all age groups had fewer relapses on the HDC.

The OS for patients treated on CALGB 9082 recapitulates the pilot study (CALGB 8782) and is better than prior SDC studies in CALGB (CALGB 8082, 8541). The current study compares HDC to IDC and not standard dose therapy. The current data do not yet establish HDC as superior to SDC. However, as the data have matured, statistically significant differences in favor of HDC have developed [70].

The study randomized 154 women: 75 women received two courses of high-dose cyclophosphamide, mitoxantrone, and etoposide (CNEV) with PBPCCT while 79 patients were randomized to receive six cycles of CAF. This study compares HDC and SDC directly. Median follow-up is 5.3 years and is the most mature of the currently presented HDC studies in primary disease (Fig. 1). There was a significant reduction in the number of relapses in favor of transplant (28% versus 69%). Both RFS and EFS were statistically superior for patients on the HDC arm.

The third study presented was from the Scandinavian group. Five hundred and twenty-five patients were randomized to receive either nine courses of an escalated FEC regimen or two cycles of conventional FEC followed by a modified FEC, followed by HDC, in the form of CTCb. The follow-up on the study is extremely short at 20 months (Fig. 1). Metastases were not aggressively excluded as in the CALGB and other studies. This may have contributed to the high early relapse rate in the study. There have been 133 relapses (25%) among patients enrolled. Of great concern is the occurrence here of seven cases of acute myeloid leukemia or myelodysplastic syndrome on the nontransplant arm. As was noted by discussant Dr. Karen Antman, the Scandinavian study uses escalated doses resulting in a threefold increase of 5-flourouracil (5-FU), a 5.5 times excess of epirubicin and, a 1.4-fold increase in cytoxan on the tailored FEC “standard arm.” This makes comparison between the HDC and SDC arms difficult to interpret.

Two other studies have been previously communicated from the Dutch group and the M.D. Anderson Cancer Center study. The former study involved 81 breast cancer patients.
with an involved axillary lymph node on a random biopsy that underwent neoadjuvant chemotherapy with FEC followed by surgical excision and axillary dissection. Patients were then randomized with both arms receiving an additional FEC cycle and one arm a CTCb HDC regimen. It showed no difference in terms of EFS or OS. The study was only powered to detect a difference of approximately 35%, and had the inherent problem that approximately 15% of patients deviated from assigned treatment but were included in the intention-to-treat analysis. The M.D. Anderson study closed early due to slow accrual and involved only 78 patients. The design was for all patients to receive eight cycles of FAC with one-half of the patients randomized to receive two additional courses of high-dose cyclophosphamide, etoposide and cisplatin (CEP) with PBPC. Again, no significant differences in DFS or OS were seen. Problems with patient compliance with the randomization and the size of the study limit its ability to provide useful guidance for clinical care.

With the marked reduction in morbidity and mortality, the reduction in costs and the early indications of a positive impact of HDC and PBPC, as well as the fact that patients with fewer than 10 positive lymph nodes often have a poor outcome to SDC, a prospective randomized phase III, National Cancer Institute sponsored intergroup trial (SWOG 9623) is being conducted comparing HDC and PBPC with an involved axillary lymph node on a random biopsy that underwent neoadjuvant chemotherapy with FEC followed by surgical excision and axillary dissection. Patients were then randomized with both arms receiving an additional FEC cycle and one arm a CTCb HDC regimen. It showed no difference in terms of EFS or OS. The study was only powered to detect a difference of approximately 35%, and had the inherent problem that approximately 15% of patients deviated from assigned treatment but were included in the intention-to-treat analysis. The M.D. Anderson study closed early due to slow accrual and involved only 78 patients. The design was for all patients to receive eight cycles of FAC with one-half of the patients randomized to receive two additional courses of high-dose cyclophosphamide, etoposide and cisplatin (CEP) with PBPC. Again, no significant differences in DFS or OS were seen. Problems with patient compliance with the randomization and the size of the study limit its ability to provide useful guidance for clinical care.

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**HDC For Metastatic Breast Cancer**

Tannock and his colleagues reported a dose-response relationship in standard regimens administered to women with metastatic breast cancer [71]. Unfortunately, the doses employed were relatively low and the findings represented threshold dose effects. A clear dose-response effect was seen with intensification of ifosfamide in combination with cisplatinum and etoposide without cellular support [72]. A recently reported study suggested that modest dose intensification of paclitaxel did not result in improved outcome [73]. On further review there is currently little to indicate that this agent either lends itself to meaningful dose escalation or that it exhibits a steep dose-response curve. In addition to the modest escalation, the total dose received in each group after toxicity-related adjustments has yet to be reported.

In the early 1980s, phase I/II trials of HDC and transplantation for metastatic breast cancer were undertaken. A series of 1,367 patients who had received active second-line combinations of drugs at standard doses as salvage therapy served as a useful comparative group. This salvage approach resulted in an overall response rate of 33% + 14% [74]. The average duration of response was 6.7 months, and median survival 8.5 months. Patients entered into the phase I/II HDC trials of dose intensification often had failed such salvage. The phase I HDC data indicated that the frequency of objective response was significantly higher (approximately 70%) than observed with SDC salvage regimens [75-77]. Indeed, complete responses were observed in 17% to 37% of patients. The objective response rate to HDC was 2 to 10 times greater than for SDC, even though SDC patients had received less prior chemotherapy. However, as with SDC in advanced disease, durable remissions were rare.

Phase II trials of HDC without induction therapy established that long-term DFS could be produced in a percentage of patients. In updated data from Peters and coworkers [78], 3 of 22 (14%) poor-prognosis premenopausal patients who were estrogen receptor-negative, and had visceral dominant disease remain continuously disease-free at full performance status with minimum follow-up of 11 years and lead follow-up at 14 years.

Consistent with the third of Skipper’s rules, bulky metastatic disease might limit efficacy of HDC. Consequently the strategy of employing induction chemotherapy to reduce tumor burden prior to HDC and PBPC was evaluated. While induction therapy appears to increase the complete response rate and to prolong the relapse-free interval, long-term DFS rate appears to be on the order of 20% to 30% with or without an induction regimen [4].

The favorable initial results of HDC prompted several groups to treat patients with this approach at relapse after therapy for primary disease. Patients in these series generally were young, premenopausal women, who were initially estrogen receptor-negative or hormone manipulation-refractory and who had measurable visceral disease. In contra-distinction to many SDC trials, prior adjuvant chemotherapy was usually permitted. A large number of such phase II HDC studies have now been reported [79-99]. The data in aggregate suggest that a single course of HDC will result in complete responses 30%-50% of the time and overall responses in approximately 80% of patients with metastatic breast cancer.

ABMTR reported outcomes for HDC in metastatic disease are consistent with the reported phase II data [43].

There are now four available randomized studies in metastatic breast cancer. Two, including the study by Peters and his colleagues [100] (the adriamycin fluorouracine methotrexate [AFM] randomized trial) and the study from Bezwoda and his coworkers [101] from South Africa, have been presented previously at ASCO. Both demonstrated improvement in EFS for patients receiving high-dose therapy compared to standard dose therapy alone (South African study) or as consolidation after an intensive standard therapy (AFM randomized trial). There were two studies presented at the 1999 ASCO meeting which bear on the analysis of high-dose therapy in metastatic disease. The summary data and the previously reported randomized studies are summarized in Table 2.
The first study presented at 1999 ASCO, known as the “Philadelphia” trial or PBT-1, enrolled 553 patients and has a median follow-up of three years. This study randomized patients to receive either six cycles of CAF or four to six cycles of CMFP. Patients were then restaged. Patients with either a partial or complete response were randomized to receive consolidation with CTCb and a stem cell transplant or two years of CMF therapy. The design as well as the numbers of patients involved at each step are shown in Figure 2. It is important to note that the study had a significant dropout rate at each point along the way. Only 57% or 296 total patients of the initial 553 achieved a response. Eleven percent achieved a CR and the PR rate was 47%. With patients dropping out of the study, refusing to be randomized or for other reasons, only 33% of the original patients or 184 patients were randomized. The randomization was unbalanced with 101 patients randomized to the HDC arm and 83 to the CMF arm. Ten patients randomized to the SDC arm were actually transplanted. Three received no therapy. Because of the intention-to-treat analysis, all of these were analyzed as part of the CMF arm. Five patients on the HDC arm received no therapy; one patient was transplanted off study.

The study demonstrated no difference in EFS, time to progression (TTP), or OS. The median TTP for the transplant group was 9.6 months and for the CMF group 9.0 months ($p = 0.31$). The median OS for the HDC group was 24 months, and 26 months, ($p = 0.23$) for the CMF group.

The conversion rate for patients from PR to CR in the study by HDC was extremely low. Seventy-two patients with a PR to the induction therapy were randomized to HDC and only five were converted to CR (6%). On the SDC arm of CMF, six were converted to CR (9%). This conversion rate to CR is extraordinarily low with an overall 13% CR rate for patients on the study. These data are in stark contrast to the usual results obtained in metastatic breast cancer using HDC where the CR rate ranges from 39% to 64% with an overall analysis of 58% achieving a CR [100, 104-106].

The results that have been obtained in PBT-1 are below the standard achieved in prior and contemporary studies. The high dropout rate in the study clouds any potential extrapolation of the results to a general population. Thirty-three percent of responders dropped out before randomization; 11% more dropped out after randomization. In addition, there was a very low CR rate overall obtained in the study. Eleven percent of patients had a CR to the induction therapy. Only 13% of all patients entered on the study achieved a CR. HDC with CTCb and PBPC produced inferior results compared to other HDC studies. Most who have examined the data from high-dose studies conclude that HDC is clearly able to increase the frequency of CR. The conversion from PR to CR by HDC of only 6% is lower than almost any other study of sufficient size that we have been able to find in the literature. It is further important to note that patients were eligible to be entered on study after they had received chemotherapy and that eligibility was determined by a retrospective review of staging tests. This scientific design is unusual in the conduct of most clinical studies. One other key point is the suggestion that more of those on the HDC arm

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### Table 2. Randomized studies of HDC in metastatic breast cancer

<table>
<thead>
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<th>PI/study/regimen</th>
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<tr>
<td>Peters: AFM Randomized Trial (CPB) [100]</td>
<td>425</td>
<td>9 yrs</td>
<td>Improved EFS for CR patients transplanted immediately; delayed HDC had better OS for CR patients; 12% TRM</td>
</tr>
<tr>
<td>Bezwoda: South African Study (CNV) [101]</td>
<td>90</td>
<td>5 yrs</td>
<td>Improved DFS and OS; direct comparison HDC to SDC</td>
</tr>
<tr>
<td>Stadtmauer: PBT-1 (CTCb) [102]</td>
<td>533/184</td>
<td>3 yrs</td>
<td>&gt;60% dropout; poor CR 13%; equivalent DFS/OS; 9-month TTF; no TRM</td>
</tr>
<tr>
<td>Lotz: Pegase 04 (CMA) [103]</td>
<td>61</td>
<td>5 yrs</td>
<td>Doubled median DFS; $p = 0.06$; DFS and OS curves come together at 5 years.</td>
</tr>
</tbody>
</table>

EFS = event free survival; CR = complete response; OS = overall survival; TTF = time-to-treatment failure; TRM = treatment related mortality.

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**Figure 2.** Shows the PBT-1 Study Schema as well as the numbers of patients involved at each step of the study.

The results that have been obtained in PBT-1 are below the standard achieved in prior and contemporary studies. The high dropout rate in the study clouds any potential extrapolation of the results to a general population. Thirty-three percent of responders dropped out before randomization; 11% more dropped out after randomization. In addition, there was a very low CR rate overall obtained in the study. Eleven percent of patients had a CR to the induction therapy. Only 13% of all patients entered on the study achieved a CR. HDC with CTCb and PBPC produced inferior results compared to other HDC studies. Most who have examined the data from high-dose studies conclude that HDC is clearly able to increase the frequency of CR. The conversion from PR to CR by HDC of only 6% is lower than almost any other study of sufficient size that we have been able to find in the literature. It is further important to note that patients were eligible to be entered on study after they had received chemotherapy and that eligibility was determined by a retrospective review of staging tests. This scientific design is unusual in the conduct of most clinical studies. One other key point is the suggestion that more of those on the HDC arm
had received adjuvant chemotherapy than on the SDC arm. This has been identified as a significant negative prognostic indicator [4]. Information about the quality of life and the costs of each of the arms may prove useful in placing this study in appropriate context since with similar outcomes, patients may prefer (and it may cost less) a short treatment modality to an extended one over two years.

The second randomized clinical trial presented at the ASCO meeting in metastatic breast cancer was from France, the Pegase 04 study. In this study patients with metastatic breast cancer responding after four to six cycles of conventional therapy were randomized to receive either HDC (cyclophosphamide, mitoxantrone, and melphalan [CMA]), or two to four additional cycles of the same conventional chemotherapy. Time to progression was nearly doubled for patients receiving HDC (36 months versus 18 months). Because the relapse rate at five years was not different, the data are not statistically significant. Similar results were seen in OS with a median of 18 months on the SDC arm and 36 months on the HDC arm. Because of small sample size, the data only approached statistical significance ($p = .06$).

An overview of trials in metastatic breast cancer using a meta-analysis technique was performed by Dr. Karen Antman and the statistical group from Columbia University Biostatistical Center on the available randomized data in metastatic disease. Analysis of all trials together demonstrated a statistically significant difference ($p = 0.049$) in favor of high-dose therapy across all the randomized studies performed in metastatic breast cancer.

One other study meriting some comment was the statistical evaluation performed by Berry and colleagues where ABMTR HDC data and CALGB SDC data in metastatic disease were compared [107]. While initially reported as showing equivalence, this study reflected primarily CTCh-treated patients since this is what dominates the registry data. The analysis has subsequently been extended to patients receiving CPB and the results reflect potential differences in treatment regimens.

**SCHEDULE OF HDC AND PBPCT**

The AFM randomized trial introduced an additional important variable when it evaluated HDC schedule in patients achieving a CR after intensive induction therapy using doxorubicin, 5-FU and methotrexate (AFM) [100]. Four hundred and twenty-three patients with hormone-insensitive, measurable metastatic breast cancer who were chemonaïve for metastatic disease were entered into the study. After initial evaluation, patients received two to four cycles of AFM at 21-day intervals. The response to AFM was defined after the second, third and fourth cycles. One hundred and five patients (25%) reached CR. Ninety-eight were randomized to either undergo immediate HDC (CPB) with transplantation or be closely observed. Randomization was balanced for pretreatment characteristics and site and extent of disease. Patients receiving HDC exhibited a DFS threefold better than that of the observation group ($p < .0001$). EFS was 24% at five years for patients who had received the HDC versus 8% for the closely observed patients. It is of note that retrospective evaluation of patients who were felt to meet transplant eligibility criteria and received SDC (CAF) had an almost identical five-year progression-free survival of 8% [108].

In the AFM study, patients relapsing on the observation arm were taken to CPB and PBPCT. The provocative finding was that the patients receiving AFM chemotherapy, achieving a CR, and undergoing high-dose CPB at relapse had significantly better survival compared to the patients receiving immediate transplant. Median OS of the patients undergoing immediate HDC was 2.25 years compared with 3.56 years for those treated with HDC at relapse. Beyond seven years patients having the delayed transplant have an OS in excess of 37%—better than that of the patients transplanted immediately. This difference does not relate to higher TRM; indeed there was no difference in terms of TRM between the immediate and delayed transplant groups.

These findings appear at first blush counter to Skipper’s inverse rule, which implies that small tumor burdens are more curable. However, just as larger tumors have a higher propensity to intrinsic drug resistance, so too, is it probable that induction chemotherapy induces cellular or functional resistance which may decrease with the passage of time. This may help explain the striking results produced in both of the Bezwoda studies with up-front transplantation.

**QUALITY-OF-LIFE ISSUES**

Initial evaluations employing the Functional Living Index-Cancer and Symptom Distress Scale in patients receiving HDC and PBPCT [109], found that quality of life appeared comparable to patients receiving SDC. Few patients reported functional limitation a year or more after transplant [110]. A number of studies comparing transplanted patients with normal subjects describe impaired self-rated physical function, fatigue and sexual dysfunction [111-113]. Normal subjects are, however, an unsuitable control group and when compared with cancer patients receiving SDC, quality-of-life measures in transplant patients are frequently equivalent or superior [114]. Indeed, the recently preliminarily reported CALGB 9082 had a companion quality-of-life analysis which was communicated at 1999 ASCO [115]. While transplant patients had inferior quality-of-life assessments at three months after HDC, by six months and a
year the analysis revealed equivalence between the HDC and IDC arms.

**Perspective After the Initial Randomized High-Dose Data**

It must be rigorously understood that each of the randomized studies thus far communicated ask a different question and depending upon the intensity of HDC regimen, the intensity and duration of the “SDC” control and the schedule of events in relation to induction chemotherapy, the outcomes may be quite variable. Certain general trends are identifiable. No study has shown transplant to be an inferior option. The randomized data thus far show CTCb HDC and PBPCT to be equivalent to dose-escalated FEC or CMF administered for two years. Taken in aggregate it appears that CTCb is a relatively ineffective regimen. Other HDC regimens including CPB, CNV and CMA have shown superiority in randomized studies in certain outcome endpoints over SDC. In some of these studies significantly longer follow-up is required before definitive analysis can be completed.

Further evaluation of up-front HDC may be of critical importance in defining its role in the treatment of breast cancer. Both South African studies in metastatic disease and primary disease demonstrated a significant value to the use of HDC as the initial treatment. The AFM randomized trial demonstrated that high-dose therapy after a delay in patients who had achieved a CR resulted in superior OS. The reasons for this may relate to the possibility that initial SDC produces either transient or functional resistance, or adversely affects the PK and PD of the HDC. Evaluation of the appropriate timing of HDC appears of critical importance in defining its eventual role.

It is also clear that HDC alone will not completely solve the problem of breast cancer, but still should be considered as part of an overall therapeutic plan for patients with the disease. Novel therapeutic advances, including antibodies, vaccines, biological response modifiers and new drugs, will all need to be evaluated for their potential to eliminate minimal residual disease.

Finally, it is quite clear that the media coverage surrounding and subsequent to the May 1999 ASCO meeting has had a detrimental effect on the ability to conduct trials in this area. Accruals to clinical research studies have dropped significantly, and the ability to understand the role of HDC may be forever compromised by the premature release and negative criticism of these preliminary data. Science is not best conducted in the New York Times or by NBC News. The optimal analysis of HDC is by careful scientific discourse after systematic consideration of the data. The current data indicate that above all there is no substitute for adequate follow-up. With the exception of the Philadelphia study and the study from South Africa, there is not adequate follow-up for any of the studies presented during the plenary session at ASCO. Thus we will simply have to wait for time to allow the full analysis of the treatment results. It will be very difficult to overcome the negative impact of the media. Women who are in the course of treatment or facing this dire diagnosis are confused by the information being presented in the popular literature. Their physicians are frequently confused by the data. Of even more concern is the fact that at the present time there is no prospective randomized cooperative group study available within the USA for patients either with metastatic breast cancer or 10 or more positive nodes. There is one study available to patients with four to nine positive nodes as an intergroup study, but accrual to this has fallen precipitously since the ASCO publicity.

**Addendum**

As this paper is going to press, the University of Witwatersrand in Johannesburg, South Africa has informed ASCO of a University investigation into alleged “serious scientific misconduct” in the adjuvant high-dose study conducted by Dr. Werner Bezwoda. The chief of the Witwatersrand University’s Committee for Research on Human Subjects stated that there were admissions of “a serious breach of scientific honesty and integrity” in the study and recommended that the results should “not be used as a basis for further trials.” Until such time as this investigation is completed, we agree completely with this recommendation, caution the reader about any interpretation of the Bezwoda report or conclusions based upon that data, and reiterate our long-standing position that well-designed and executed clinical research studies, especially randomized studies, remain the best treatment option for patients with cancer, and should be the way patients are considered for high-dose therapy.

Editors’ Note: see page 17.
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