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Clinical results in 2001 show high dose therapy and hematopoietic progenitor cell transplantation as a therapeutic option for breast cancer

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Presentations of phase III trials evaluating high dose therapy (HDC) with autologous hematopoietic progenitor cell transplantation (APCT) for breast cancer (BC) at the recent *American Society of Clinical Oncology* (ASCO) Meetings prompted us to comment on their results and review previously available clinical data. In the last decade, we have observed very peculiar highs and lows in the enthusiasm of clinicians for HDC with APCT for treatment of BC. Early trials of HDC, based on favorable laboratory and clinical indicators,[1,2] initiated in the 1980s, suggested that HDC with APCT might favorably affect the course of operable high-risk and metastatic BC.[3] Phase II studies created positive expectations among physicians and their patients, to such an extent that HDC with APCT became widely used as a therapeutic option also outside controlled trials. Simultaneously, many phase III studies were initiated. The use of blood cells instead of bone marrow for APCT[4,5] significantly reduced the morbidity and mortality related to HDC[6,7] and allowed the spread of this procedure also outside specialized centers.

At the 1999 ASCO Meeting, findings from small or prematurely reported randomized trials were presented (*abstracts 1-4, 161, Proceedings book*). These trials did not show unequivocally positive results and their superficial consideration caused a barrage of negative reports from media[8] and oncologists[9] suggesting to many patients and physicians final conclusions disparaging of this therapy. The subsequent demonstration that the South African adjuvant study[10] was fraudulent[11] had an additional detrimental effect on accrual to ongoing randomized trials.[12] At the 2000 and 2001 ASCO Meetings, new information was provided from phase III trials of HDC for BC. In this article we review and comment on the data from randomized studies so far reported and try to indicate what could be next in this story. We also suggest what may be the attitude we should take in our everyday clinical practice.

Operable, high-risk breast cancer (adjuvant therapy)

In the early 1990s phase II studies from several centers and the European and American registries showed a 60-65% disease-free survival (DFS) for patients with high-risk operable BC at 4-5 years post-transplant.[13-15] Since these data appeared better than those following standard dose therapy, several centers and co-operative groups began phase III trials, comparing transplant to best available conventional therapy. Two early phase III randomized studies from the Netherlands Cancer Institute and the MD Anderson Cancer Center have been published.[16,17] No advantage of HDC has emerged. However, both studies were designed to detect an optimistic 30% difference in relapse-free survival (RFS) between high-dose versus conventional adjuvant therapy and were too small (81 and 78 patients randomized, respectively) to assess smaller differences that cannot be excluded.[18] In this regard it is interesting to note that, in the subsequent larger Netherlands Cancer Institute phase III study, the HDC arm gave an overall survival (OS) benefit of about 10% in the first 284 patients studied, as detailed below in this article. After excluding a misleading and unreliable trial,[11] to date 5 randomized studies with large patient accrual have been either published or presented at the 2000 and 2001 ASCO Meetings (Table 1).

The Scandinavian Study Group multicenter trial[19] randomized 525 high risk primary BC patients to receive 3 cycles of fluorouracil (5-FU), cyclophos-

Table 1. Summary of randomized studies of HDC with APCT as adjuvant therapy for high-risk breast cancer.

Study group and leader investigator ref.	*Patients (n)*	*Median follow-up (years)*	*Results*	*Comment*
Netherlands Cancer Institute, S Rodenhuis[16]	81	4.5	No survival benefit	Designed for detecting an optimistic 30% advantage; small study; poor patient compliance with randomization
MD Anderson, G Hortobagyi[17]	78	4	No survival benefit	Designed for detecting an optimistic 30% advantage; small study; protocol treatment deviation; closed because of slow accrual.
Scandinavian Study Group, J Berg[19]	525	3	DFS favors control arm; OS same	Control arm not conventional tailored chemotherapy, total dose of the non HDC arm higher; high incidence of MDS/AML in the control arm; longer follow-up required
Netherlands Cancer Institute, S Rodenhuis[20]	885, first 284 patients evaluated	3.5	Significant improvement in DFS and OS in the HDC arm	Evaluation of the whole study population required; TRM < 1%. Longer follow-up required
CALGB, WP Peters[21]	785	5.5	No difference in EFS and OS	31% mortality reduction; high TRM, center- and age-depen dent; control arm not conventional; patients < 50 years of age have better outcome (no statistical analysis provided so far). The study requires longer follow-up
Milan Cancer Institute, AM Gianni[22]	382	5	EFS and OS same	TRM < 1%; favorable trend in DFS in younger patients and 4-9 axillary nodes; short duration of the HDS arm. The study requires longer follow-up
French PEGASE, HH Roche[23]	314	3	Significant improvement in DFS; no difference in OS.	Short follow-up; risk reduction for OS, DFS and event free survivals.

phamide (CTX) and epirubicin (FEC) at standard doses followed by HDC with the STAMP-V regimen (CTX 6 g/m^2, thiotepa 500 mg/m^2, and carboplatin 800 mg/m^2) and APCT or nine cycles of FEC tailored to individual tolerance (up to 1800 mg/m^2 of CTX, 120 mg/m^2 of epirubicin and 600 mg/m^2 of 5-FU per cycle) with granulocyte colony-stimulating factor (G-CSF) support. The control arm was not given a standard dose according to any widely accepted definition. Patients in the non-HDC arm received higher cumulative doses of alkylating agents and had a higher incidence of treatment-related leukemia and myelodysplastic syndromes. At a median follow-up of less than 3 years (somehow too short for any BC adjuvant trials) tailored FEC resulted in an improved DFS (p=0.04) with no difference in OS between the two study arms.

The Netherlands Cancer Institute multicenter trial randomized 885 patients with more than 4 nodes at surgery to receive 5 courses of FEC versus the same chemotherapy followed by HDC with CTX 6 g/m^2, thiotepa 480 mg/m^2 and carboplatin 1600 mg/m^2 with APCT. The high dose regimen is similar to the STAMP V regimen, but it contains a double dose of carboplatin and the 3 alkylating agents are given by short rather than continuous IV infusion. The first analysis planned in the study protocol evaluated the first 284 randomized patients[20] and found that DFS and OS were significantly improved in the HDC arm (77% vs 62%, p=0.009 and 89% vs 79%, p=0.039, respectively).

The CALGB-9082 multicenter phase III trial[21] enrolled 785 patients with 10 or more positive axillary nodes to receive 4 cycles of CTX, doxorubicin, and 5-FU followed by either HDC with STAMP-I (cyclophosphamide, cisplatin, and BCNU at 5625, 165, and 600 mg/m^2, respectively) versus a single cycle with the same drugs at intermediate doses (900, 90, and 90 mg/m^2, respectively). The inclusion of this cycle in the control arm is evidence of the investigator's desire for trial design symmetry. At a median follow-up of 5.5 years both event-free and OS were unexpectedly high (better than observed in any prior study within the CALGB). The number of relapses was higher in the standard arm than in the HDC arm (167 versus 127, -31%), counterbalanced by an increased transplant-related mortality (TRM) in patients receiving HDC (7.4%). TRM positively correlated with older patient age and size of HDC activity of participating centers. In this

study, in which the sample size was planned to detect a 14% reduction of RFS at 5 years, DFS favored HDC but did not reach statistical significance. Furthermore, in the HDC arm women <50 years old had improved RFS. At the 2001 ASCO Meeting results of statistical analysis of the latter subgroup were not presented.

The Milan National Cancer Institute multicenter phase III trial[22] enrolled 382 patients with 4 or more involved axillary nodes comparing adjuvant standard-dose (epirubicin 120 mg/m^2 for 3 cycles followed by CTX, methotrexate, 5-FU (CMF) for 6 cycles) with sequential high-dose chemotherapy (HDS, CTX 7 g/m^2; vincristine 2 mg and methotrexate 8 g/m^2 with leucovorin rescue; epirubicin 120 mg/m^2 q 14 days for 2 doses; and thiotepa 600 mg/m^2 plus melphalan 160-180 mg/m^2 with APCT). The study was designed with a power of 80% to detect a 15% increase in progression-free survival (PFS) at 5 years in the HDS arm. Treatment-related mortality was less than 1%. PFS and OS at 5 years were similar in the two treatment arms. Among the 112 patients younger than 36 years, and the 147 patients with 4-9 positive nodes, those in the HDS group showed a trend for a DFS advantage (HR 0.66 and 0.69, respectively). Since the 90% of patients in both treatment arms received 5 years of tamoxifen, the authors suggest that final analysis with a prolonged follow-up is advisable. HDS and conventional treatment lasted about 3 and 8 months, respectively.

The French PEGASE multicenter phase III trial[23] randomized 314 women with more than 7 positive nodes at surgery to receive 4 cycles of FEC100, then either no further chemotherapy or one cycle of high dose CMA (CTX 120 mg/kg, mitoxanthrone 45 mg/m^2, alkeran 140 mg/m^2) followed by radiotherapy and tamoxifen for positive hormonal receptor menopausal women. Patients and tumor characteristics were well balanced. With a median follow-up of 39 months, 123 events and 63 deaths occurred. In an intent-to-treat analysis, 3-year rates for conventional and HDC arms were, respectively, 55 and 70.8 % (p<0.003) for DFS and 84 and 86 % (p=0.33) for OS. HDC offers a significant risk reduction of 22%, 43% and 39% (p=0.007) for OS, DFS and event-free survivals, respectively.

Locally advanced and inflammatory breast cancer

Stage III B and C BC accounts for about 5% of all diagnoses but has a very high risk of distant recurrence. HDC with stem cell support has been utilized within multimodality treatment programs of primary therapy. In general all these pilot/phase II studies[24-27] have shown high rates of pathologic response and apparent advantage in DFS rates. However, the limited number of patients enrolled and the lack of randomized trials do not allow conclusions to be drawn about survival.

Metastatic breast cancer

Pilot transplant trials in BC in the early 1980s were initially conducted in metastatic disease and demonstrated high response rates for patients with measurable tumors.[28,29] This translated into an apparent improvement of survival compared with that recorded in similar groups of patients treated with conventional therapy. The observation that in studies of HDC without induction therapy long-term DFS could be produced in a percentage of patients is of particular note. Indeed, in updated data from Peters *et al.*,[29,30] a small group (14%) of poor-prognosis premenopausal patients who were estrogen receptor-negative, and had visceral dominant disease remain continuously disease-free with a minimum follow-up of 11 years. The favorable initial results of HDC prompted several groups to use this approach to treat women at relapse after therapy for primary disease. A large number of phase II HDC studies have now been reported.[31-37] Taken together the data indicate that a single course of HDC will result in 30%-50% complete responses (CR) and overall responses (OR) in approximately 80% of patients with MBC. The *American Blood and Marrow Transplant Registry* (ABMTR) reported outcomes for HDC in metastatic disease which are consistent with the reported phase II data.[15] Long-term DFS at 5 years for women receiving HDC appears to be largely superior compared to that achieved by current standard chemotherapy.[38,39] After excluding an early randomized trial[40] that was discovered to have not been conducted in a scientifically acceptable manner,[41] 4 studies have so far been released comparing HDC with APCT with conventional therapies (Table 2). Results of these studies are described in the following paragraphs.

The Philadelphia Intergroup phase III trial[42] enrolled, over a 7-year period, 513 patients to receive CAF (no prior anthracycline therapy) or CMF salvage chemotherapy followed by randomization for those in CR or partial remission (PR) to receive either a transplant using the STAMP V regimen or maintenance CMF for up to 24 cycles (2 years of chemotherapy) or until progression. With patients dropping out of the study, refusing to be randomized or for other reasons, only 33% of the original patients (184) were randomized. The randomiza-

Table 2. Summary of randomized studies of HDC with APCT in patients with metastatic BC achieving response to conventional first line therapy.

Study group and leader investigator(ref.)	*Patient (n)*	*Median follow-up (years)*	*Results*	*Comment*
Philadelphia-Intergroup, EA. Stadtmauer[42]	553/184	5	No difference in DFS and OS	> 60% drop-out; poor conversion to CR; 13% patients in the control arm received HDC; low TRM
Dukes' study. WP Peters[43]	425/120	9	Improvement in DFS high TRM	OS not evaluable (crossover design); delayed HDC effective
Dukes' study (bone metastasis only), B Modan[44]	69	5	Improvement in DFS bone metastasis setting.	OS not evaluable (crossover design); high TRM
French PEGASE, JP Lotz[45]	61	5	Improvement in DFS, OS equivalent at 5 years	Small study
Cancer Institute of Canada, M Crump[46]	219	3	DFS prolonged, no difference in OS	High TRM; high progression rate before transplantation

tion was unbalanced (101 patients to the HDC arm and 83 to the CMF arm). Ten patients (13%) randomized to the control arm actually received HDC and three patients received no therapy. Because of the intention-to-treat analysis, all of these were analyzed as part of the CMF arm. In contrast, five patients in the HDC arm received no therapy. The Philadelphia trial demonstrated no difference in DFS (9.6 months for HDC versus 9.0 months for CMF), or OS (24 months vs 26 months). The conversion rate for patients from PR to CR in the study by HDC was extremely low; 6% in the HDC arm and 9% in the CMF arm. These data are in contrast to the usual results obtained in MBC using HDC. Overall the results that have been obtained in this study are below the standard achieved in prior and contemporary studies. Planned cumulative dose in the CMF arm exceeds that of the HDC arm. 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 well informed patients may prefer a short intense treatment modality to up to two years of repetitive cycles of chemotherapy.

In the Dukes' study[43] with a crossover design, 120 of 453 patients with MBC attaining CR with conventional dose doxorubicin, 5-FU and methothrexate were randomized to either immediate HDC with STAMP-I versus STAMP-I at the time of relapse. The authors reported that high-dose consolidation significantly delayed relapse (in some cases, preventing it altogether) in patients who were in remission following conventional chemotherapy. Patients who were randomly assigned to observation following conventional treatment, however, frequently went back into remission after high-dose salvage therapy at the time of relapse. A group of 69 women with bone metastases only underwent the same randomization with crossover to HDC for women with conventional treatment at time of relapse. A significant difference in DFS favors HDC.[44] Because of the crossover design of the Dukes' trials, OS for conventional versus HDC cannot be compared.

The French PEGASE 04 multicenter phase III trial[45] randomized 61 patients with stage IV disease in clinical response after four to six cycles of conventional therapy to receive either HDC with CMA, or two to four additional cycles of the same conventional chemotherapy. Median DFS were 20 versus 35 months in the standard and HDC groups, respectively (p=0.05). Similar results were seen in OS with a median of 20 months in the standard dose arm and 43 months in the HDC arm. Because of small sample size, the data only approached statistical significance (p=0.06). At five years, the relapse rates were nearly identical: 90.8% and 90.7%, respectively.

The National Cancer Institute of Canada phase III trial[46] randomized 219 MBC patients achieving response with first line treatment to receive 2-4 additional cycles of standard chemotherapy or 1-2 cycles followed by HDC (CTX 6 g/m^2, mitoxanthrone 70 mg/m^2, carboplatin 1800 mg/m^2) with stem cell rescue. Twenty-three of the 112 patients randomized in the HDC arm never received trans-

plantation because of progression or other causes. Seven treatment-related deaths were recorded, all in the HDC arm (7.7%). DFS was significantly prolonged in the HDC arm while no differences in 3-year OS could be documented.

The therapeutic value of HDC in perspective

Evaluation of mature data of HDC with APCT in comparison with conventional chemotherapy allows the following considerations:

1. in the adjuvant treatment of high-risk BC, among the five large adjuvant trials reviewed in this article (Table 1), two have shown an advantage for HDC and one favors the control arm. Two studies have shown favorable trends in certain subgroups of patients. In these studies a longer follow-up is required before definitive analysis can be completed;
2. in the treatment of metastatic BC, three out of the 4 studies reviewed in this article (Table 2) have shown significant differences in DFS in favor of HDC. The delay in relapse for patients treated with HDC could potentially offer a longer off-therapy survival and possibly better quality of life. Analyses of subsets of patients in CR, PR or by metastatic sites are limited due to the lack of statistical power because of insufficient number of patients;
3. in some studies the duration of HDC programs is shorter than with conventional chemotherapy.[22,42] Thus, even considering similar disease outcomes, one could argue that patients might prefer a short intense treatment modality rather than prolonged administration of conventional chemotherapy.

Overall, no study with adequate follow-up has shown HDC with APCT to be an inferior option. The outcomes of these trials have been quite variable, this partially depending on their heterogeneity. In fact, they differ in terms of disease stage, type of HDC regimen, intensity and duration of the control therapy, and the schedule of events in relation to induction. As an example, the randomized data thus far show the STAMP-V regimen to be equivalent to dose-escalated FEC or CMF administered for two years while other regimens including STAMP-I and CMA have shown superiority in certain outcome end-points over conventional treatments. It should also be taken into consideration that, in HDC programs, important therapeutic differences might be missed if biological aspects are ignored. It is well known, for example, that the dose effect is more significant in 20-30% of patients whose tumors overexpress Her2/neu.[47]

It must be remembered that almost 100% of patients with MBC, and more than 50% of patients with high-risk multinode positive disease will die from cancer, despite partially successful conventional treatment. As previously stated, high rates of durable remission, never observed by conventional treatments, are provided by long-term follow-up of studies of HDC. For these reasons continued investigation of high-dose strategies is not only advisable, but mandatory. Several randomized trials of HDC are currently either ongoing or are awaiting analysis.[48] The SWOG 9623 trial bears mentioning as it compares sequential dose-dense chemotherapy (doxorubicin, paclitaxel, and CTX) with standard doxorubicin plus CTX followed by HDC (using either STAMP-I or STAMP-V) in patients with 4 to 9 positive lymph nodes. This trial is particularly pertinent as it contains adjuvant taxane therapy and 2 different approaches of HDC are evaluated. Unfortunately, because of the alarmist media coverage of the 1999 ASCO meeting, accrual to the study has dropped significantly. Recently, growing interest has been observed for the repetitive HDC with APCT strategy in BC[49,50] and other solid tumors. Although promising, results so far produced are preliminary and this approach is under evaluation in randomized trials. Costs of the multiple transplant procedure is also a matter of debate.[51,52] In addition, new technologies offer the prospect of almost cancer-free autografts[53] and are under evaluation in prospective studies. Finally, HDC can be used as a platform on which to add novel therapies aimed at treating residual tumor. Proof of principle for such approaches could well occupy clinical researchers for many years.

Some have criticized the further development of HDC based on a higher priority for molecular targeted therapies.[54] Although clinicians wait for more effective, biologically based treatments for BC, few currently exist. The monoclonal antibody trastuzumab is effective in a subset of patients with tumors overexpressing Her2-neu and is not likely to be sufficiently effective as single agent.[55] The development and subsequent clinical evaluation of more effective targeted therapies is taking several years and, in general, they are not likely to replace standard therapies but *rather* be integrated into them. Monoclonal antibodies or other biologically based treatments including vaccines, biological response modifiers and new drugs could be incorporated into high-dose regimens, the latter being *per se* capable of remarkable and rapid tumor regression, for their potential to eliminate minimal residual dis-

ease. Stem cell transplant technology is already used to deliver new biologically based therapies.[56] Nevertheless, at the present time encouraging results of phase II studies of cell vaccination therapies for solid tumors still need either to be confirmed or compared to standard treatments in randomized trials.

While the debate and research on HDC continue, we simply have to wait for time to allow the full analysis of ongoing studies and get some more insight into novel therapeutic approaches in BC. In the meantime what is the attitude we should take when women with high risk or metastatic BC ask for advice? Whenever possible patients should be enrolled in well designed randomized trials. Outside clinical studies we find that there is some evidence from the studies presented in this article to support proposing the HDC approach to selected, well informed patients.

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