The verdict is not in yet. Analysis of the randomized trials of high-dose chemotherapy for breast cancer

YAGO NIETO

Background. The relative efficacy of high-dose chemotherapy (HDC) compared to standard treatment for high-risk primary (HRPBC) or metastatic breast cancer (MBC) constitutes an area of intense controversy among the medical oncology community. A number of randomized trials have been conducted to address this issue. In most cases, the results of these trials are premature and contradictory. Furthermore, they have often been interpreted, incorrectly in this author's judgment, as proof of lack of benefit of HDC.

Evidence and Information Sources. The results of studies published in peer-reviewed medical journals or presented in scientific meetings are discussed. In some cases, the status of the studies was determined through direct communication with the trial's principal investigator.

Results. The encouraging results of phase II trials suggested a benefit for HDC in important categories of patients with breast cancer. It has been argued that selection of patients might have been a critical factor in those studies. The results, in most cases preliminary, of numerous randomized trials in metastatic and high-risk primary disease cannot offer a definitive answer to this crucial question as of yet. Important concepts in the interpretation of these studies, such as size and statistical power, length of follow-up, magnitude of clinical benefit, and broad applicability of the results, are discussed in this review.

Conclusions. The role of HDC for HRPBC or MBC patients remains undefined. Longer follow-up and mature analyses of the randomized trials are necessary before definitive conclusions are drawn. In the meantime, it is imperative that research continues, to enhance the efficacy of the procedure through innovative strategies.

Key words: high-dose chemotherapy, breast cancer, stem-cell transplant, bone marrow transplant, randomized studies.

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From the University of Colorado School of Medicine, Denver, Co, USA.

Correspondence: Dr. Yago Nieto, MD, Ph.D., Medical Oncology/Bone Marrow Transplant Program, University of Colorado School of Medicine, 4200 East Ninth Avenue, B-190, Denver, CO 80262, USA.
E-mail: yago.nieto@uchsc.edu

Autologous hematopoietic progenitor cell transplantation (AHPCT) allows for the administration of chemotherapy with a several-fold increase in the doses. Following a wealth of observations of steep dose response *in vitro*, retrospective analyses suggested a clinical correlation between dose intensity of chemotherapy and response rate and outcome in breast cancer, both in stage II-III,[1,2] and stage IV patients.[3-5] Numerous prospective trials testing the dose-response effect in the metastatic and the adjuvant settings have not shown, in general, a clear improvement resulting from *minor* dose increments. In contrast, the use of high-dose chemotherapy (HDC) with AHPCT is based on the hypothesis that *major* dose escalations within the myeloablative range are needed to overcome tumor cell resistance and produce a meaningful clinical improvement. Stem-cell support allows for dose increases well beyond normal bone marrow tolerance, with the goal of maximally capitalizing on the dose-response curve of certain cytotoxic drugs.

The prognosis of patients with stage IV or high-risk stage II-III disease receiving conventional treatment remains poor despite advances in pharmacology and biological therapy. Metastatic breast cancer (MBC) is still incurable in virtually all patients, with median survival times after detection of metastases between 18 and 24 months.[6,7] Since the appearance of adriamycin three decades ago, there has been minimal or no progress in the outcome of these patients, as evidenced in randomized investigations of new drugs, in some cases with remarkable activity, such as the taxanes.[8-10] The only improvement in overall survival (OS) reported was observed in the trial testing the incorporation of the anti-HER2 antibody, trastuzumab, into first-line treatment, with a five-month lengthening of median OS from 22 to 27 months, albeit with significant potential for cardiotoxiciy and without a major effect on long-term outcome.[11]

Most patients with high-risk primary breast cancer (HRPBC), defined by extensive axillary node involvement (four or more positive nodes) or by inflammatory disease (IBC), relapse after surgery and conventional adjuvant therapy.[12,13] While the potential for taxanes to improve the adjuvant armamentarium generated much hope, the preliminary results reported to date testing paclitaxel,[14,15] or docetaxel[16] have failed to show a benefit in the subset of HRPBC patients. The incorporation of trastuzumab into adjuvant treatment for the minority of patients with HER2-positive tumors is currently under evaluation. During the late 1980s and early 1990s, prospective HDC trials in MBC targeted in a

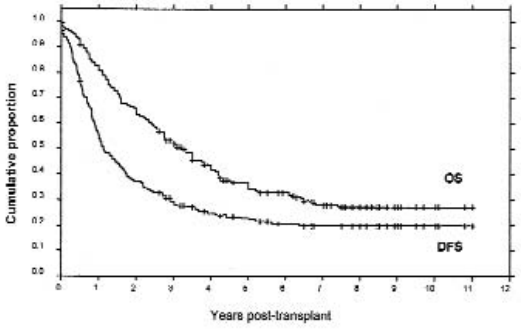

Figure 1. Long-term analysis of DFS and OS in the prospective phase II trials of HDC with cyclophosphamide, cisplatin, and BCNU, as first-line therapy for MBC patients at the University of Colorado (N=212).[23]

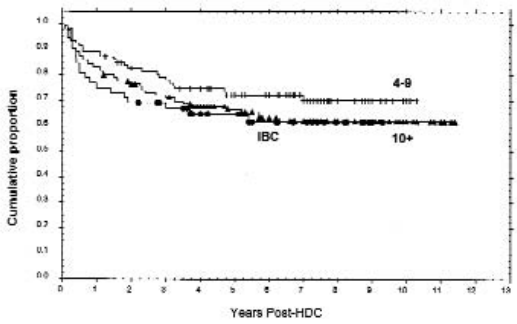

Figure 2. DFS curves of the prospective trials of HDC for HRPBC conducted at the University of Colorado. Censored patients are indicated by ▲ (≥10 + nodes, n=120), + (4-9 + nodes, n=93), or ● (inflammatory carcinoma, n=55).[31]

sequential fashion patients with refractory,[17,18] untreated,[19] and responding disease.[20-22] It soon became clear that, not only did HDC produce the highest response and complete response rates ever reported in breast cancer, but also achieved a consistent long-term disease-free survival (DFS) rate of 10-25% in patients transplanted after response to first-line chemotherapy, which appeared unprecedented (Figure 1).[23]

In parallel to these advances, the introduction of myeloid growth factors post-transplant, peripheral blood progenitor cells in place of bone marrow, and other improvements in supportive care, reduced the treatment-related mortality rate from the initial 15-20% rate to the current <5% expected in experienced transplant units.[24,25]

At the same time, Peters and colleagues at Duke University,[26] and Gianni's group at the National Tumor Institute in Milan,[27] pioneered the evaluation of HDC in HRPBC patients. At the latest update of the Duke phase II trial in patients with ten or more involved axillary nodes, 72% of patients remained free of disease at a median follow-up of eleven years after HDC with cyclophosphamide; cisplatin and BCNV (STAMP-I regimen).[28] Gianni *et al.* used a sequential high-dose single-agent approach in this population of patients.[27] At a median follow-up of four years, the DFS rate was 57%, which appeared, in retrospect, higher than that observed in the group of patients with ≥10 involved nodes receiving the most effective of two adriamycin-based standard-dose regimens compared in a separate randomized trial at the same institution, using the same selection criteria and pre-treatment staging as for their HDC trial.[29]

Similar results were subsequently reported in other HRPBC populations, such as those with four to nine involved nodes,[30] or IBC.[31,32] Importantly, long-term analyses of those trials show few late relapses (Figure 2).[33]

The percentage of patients with chemosensitive MBC or HRPBC rendered long-term free of disease after HDC appeared to be substantially higher than the expected percentage using conventional chemotherapy. These results generated great enthusiasm among physicians and patients for the use of HDC. The rapid transfer of stem-cell transplantation technology from the academic environment to community hospitals resulted in an explosive growth in the number of breast cancer patients receiving HDC. Unfortunately, many patients received HDC out of prospectively designed clinical trials, despite the lack of evidence from randomized studies demonstrating that this approach should be considered the standard of care.

Detractors of HDC argued that its promising results could be explained by biased selection of patients (younger age, better performance status), extensive staging bias, and the requirement of proven chemosensitivity.[34,35] In 1995, Dr. Craig Henderson, one of transplantation's most notorious critics, contended that *the jury was out* with respect to the value of this treatment compared to conventional management.[36] This raging controversy clearly underscored the need for mature data from prospective, well designed and adequately sized, randomized phase III trials.

Randomized trials in MBC patients (Table 1)

In the *Philadelphia* PBT-1 study, Stadtmauer *et al.* compared HDC to maintenance conventional chemotherapy in 184 patients responding to first-line therapy.[37] After initial registration of 553 patients, 303 (54%) achieved a partial (PR) (n=247) or a complete response (CR) (n=56). Of these, only 199 were randomized; 110 were allocated to the HDC arm, and 89 to receive maintenance therapy for 18 months or until disease progression. After dis-

Table 1. Randomized trials in metastatic breast cancer.

Trial (Investigator)	Population	N	F-U (mo)	DFS/PFS HDC	DFS/PFS Control	P	OS HDC	OS Control	p	Status
Canada, NCIC (Crump)[39]	Responsive	224	19	38%	24%	0.01	Med: 24 mo	Med: 28 mo	0.9	Preliminary analysis (5/01)
USA, Philadelphia (Stadtmauer)[35,36]	Responsive	184	67	5-yr: 4% Med: 10 mo	5-yr: 3% Med: 9 mo	0.3	5-yr: 14% Med: 26 mo	5-yr: 13% Med: 26 mo	0.6	Final analysis
France, PEGASE 03 (Biron)[40]	Untreated	180	48	1-yr: 46% 2-yr: 27% Med: 11 mo	1-yr: 20% 2-yr: 10% Med: 7 mo	0.00002	1-yr: 82% 3-yr: 38% Med: 29 mo	1-yr: 82% 3-yr: 30% Med: 24 mo	0.7	Preliminary analysis (5/02)
Duke Crossover 1 (Peters)[43]	CR	100	75	6-yr: 25% Med: 9.7 mo	6-yr : 10%(*) Med: 3.8 mo	0.00006	N/E (#)	N/E (#)	N/E (#)	Preliminary analysis (5/96)
Germany (Schmid)[42]	Untreated	92	14	Med: 14 mo	Med: 10 mo	0.05	Med: 28 mo	Med: 25 mo	0.3	Preliminary analysis (5/02)
Duke Crossover 2 (Madan)[45]	HR, Bone only	69	59	17%	9% (*)	0.001	N/E (#)	N/E (#)	N/E (#)	Preliminary analysis (5/00)
France, PEGASE 04 (Lotz)[41]	Responsive	61	NR	Med: 35 mo	Med: 20 mo	0.06	5-yr: 30% Med: 43 mo	5-yr: 18% Med: 20 mo	0.1	Final analysis
Germany, GEBDIS (Kanz)	Responsive	350								Accruing

NCIC: National Cancer Institute of Canada. PEGASE: Programme d'Étude de la Greffe Autologue dans les Cancers du Sein. GEBDIS: German Breast Cancer Dose Intensity Study. F-U: follow-up. NR: Not reported. HR: hormone refractory. CR: complete response. (*) DFS and PFS rates are after salvage HDC in the observation arm. N/E (#): not evaluable for a direct OS comparison between HDC and conventional chemotherapy, due to the crossover design of the studies.

carding 15 patients who were considered ineligible after randomization, 184 were actually treated in study, 101 in the HDC arm and 83 in the control arm. In the latest update of this trial with a median follow-up of 67 months, an intent-to-treat analysis showed no differences between the transplant and control arms in progression-free survival (PFS) (4% and 3%, respectively) or OS rates (14% and 13%, respectively).[38] A significant interaction was detected between age and treatment, with the death hazard in the CMF arm being 28% lower and 38% higher for those patients above and below 43 years of age, respectively.[39] This trial has received numerous criticisms. First, it lacked sufficient power to detect clinically relevant differences: while it was originally designed with an 85% power to detect a doubling in median OS time, it was subsequently limited by a 45% drop-out rate (34% before and 11% after randomization). Second, only 45 patients in CR were treated in study, conferring only a 20% power to detect a 20% absolute OS difference in this subset.[40] Since these patients, as well as those with low tumor burden, seem to be those who may benefit most from HDC, this is an important limitation of this trial. Finally, the PR to CR conversion rate was surprisingly higher in the maintenance arm with cyclophosphamide, methotrexate and fluorouracil (CMF) than in the HDC arm (9% and 6%, respectively). This strikingly low PR to CR conversion rate in the transplant arm of the Philadelphia study is quite different from that in the vast majority of phase II HDC trials, in which PR to CR conversion rates of 20-60% are typically reported.

In the trial conducted by the National Cancer Institute of Canada, Crump *et al.* randomized 224 responsive MBC patients to additional chemotherapy or HDC.[41] In this trial, 23 of the 112 patients randomized to the HDC arm were never transplanted, for a 20% drop-out rate. Transplant-related mortality was 7.7%. In the first intent-to-treat analysis at a short median follow-up of 19 months, significant differences in favor of the transplant arm were observed in DFS (38% vs. 24%, p=0.01), but not in OS (p=0.9). It is clear that a more mature analysis of this study after longer follow-up is necessary.

Similar observations were made in the first analysis of the French National trial PEGASE-03.[42] Biron *et al.* randomized 180 patients who responded to first-line conventional treatment to HDC (N=89) or observation (N=91). The acceptable 10% drop-out rate and low 1% transplant-related mortality of this trial are to be praised. At a median follow-up of 48 months, statistically significant and

fairly large differences in DFS were observed in favor of HDC compared to the control arm: 1-year DFS rate of 46% vs. 20%, 2-year DFS rate of 27% vs. 10%, with median DFS times of 11 vs. 7 months (p=0.0002). No significant differences in OS were yet observed in this first analysis: 1-year OS 82% in both groups, 3-year OS 38% vs. 30%, and median OS times of 29 vs. 24 months (p=0.7).

Some other very small studies have been reported. In the French PEGASE-04 trial, Lotz *et al*. randomized 61 responding MBC patients to additional conventional chemotherapy or HDC.[43] There appeared to be large differences in favor of the transplant arm in PFS (median 35 vs. 20 months), and OS (median 43 vs. 20 months, and 5-year OS rates 30% vs. 18%), none of which reached statistical significance (p=0.06 and 0.1, respectively) due to the very limited power of the trial. Schmid *et al*. compared tandem cycles of HDC to conventional treatment with adriamycin/paclitaxel in 92 untreated MBC patients.[44] The CR rate and time to progression were significantly superior in the transplant arm, without significant differences in OS at a very short follow-up of 14 months. While a benefit from HDC is suggested by these two trials, their very small sample sizes clearly limits their ability to detect potentially meaningful differences.

Finally, the Duke University group conducted two small randomized trials with a crossover design, comparing early versus late use of HDC in MBC patients in CR and with bone-only disease, respectively. In the first trial, Peters *et al*. randomized 100 hormone-refractory MBC patients who had achieved CR with AFM to immediate transplant with STAMP-I or to observation.[45] Patients in the observation arm were offered HDC at the time of relapse. At a median follow-up of 6.3 years, median DFS times were 9.7 months for the immediate transplant arm, and 3.8 months for the observation arm (p=0.006), with six-year DFS rates of 25% and 10%, respectively. Median OS times for the immediate transplant and observation arms were 2.34 years and 3.57 years, respectively (p=0.32), with six-year OS rates of 33% and 38%, respectively.[46] The second Duke trial randomized 69 patients with hormone-refractory bone-only MBC treated with first-line chemotherapy, to immediate HDC and radiotherapy of all bony metastases, or to radiotherapy and observation.[47] At a median follow-up of 4.9 years, all 34 patients in the observation arm had progressed; most of them subsequently undergoing salvage transplant. The progression-free survival rates significantly favored immediate transplant (17% vs. 9%, p=0.001). The OS rates were not significantly different between the immediate and late transplant arms (28% vs. 22%).

In summary, currently available results in MBC are contradictory. A benefit in DFS in favor of HDC has been noted in six of the seven trials, with the only exception being the Philadelphia study. Longer follow-up is needed to see whether the DFS advantage translates into an OS benefit. The lack of a direct comparison between a HDC arm and a non-HDC control arm complicates the interpretation of both the Duke trials. They both showed that early HDC improves DFS or PFS in those populations, but the OS analysis is obviated by the fact that patients in the observation arms were subsequently salvaged with HDC.

Randomized trials in high-risk primary disease (Table 2)

The first comparative adjuvant results came from two very small randomized phase II trials. In the trial by Rodenhuis *et al*., 81 patients with axillary level III involvement received neoadjuvant chemotherapy, followed by surgery, one more cycle post-operatively, and were then randomized to HDC or observation.[48] The final intent-to-treat analysis of the trial, at a median follow-up of 7 years, did not show significant differences between the HDC and control arms in DFS or OS. This study employed a non-standard procedure, an infraclavicular single lymph-node biopsy, to determine eligibility, instead of a standard axillary node dissection to ascertain the number of nodes involved. Hortobagyi *et al*. randomized 78 patients, with ≥10 positive nodes after upfront surgery or ≥4 positive nodes after pre-operative chemotherapy, to eight cycles of adriamycin-based treatment, followed by two cycles of DICEP (cyclophosphamide, etoposide, and cisplatin) or no further therapy.[49] This trial was prematurely closed due to slow accrual. At a median follow-up of 53 months, DFS and OS were not significantly different between both arms. The DICEP regimen has been proven to be non-myeloablative,[50,51] and is not considered HDC by most experts. It is worthwhile noting that these two small studies were only marginally powered to detect *absolute* outcome differences of at least 30%, which, if present, would have been of a greater magnitude than the overall impact of adjuvant chemotherapy for breast cancer compared to no treatment at all. Thus, neither of these two small studies contributes meaningfully to our understanding of whether HRPBC patients benefit or not from HDC.

The first preliminary analyses of larger phase III trials have been reported. In the Intergroup CALGB 9082 trial, Peters and colleagues enrolled 785 patients with ≥10 positive nodes, who received 4 cycles of CAF and were randomized to HDC with cyclophosphamide, cisplatin, and BCNU or to one additional cycle of those drugs at intermediate doses (ID) with granulocyte colony-stimulating factor (G-CSF) support.[52] Twenty-five patients who relapsed in the intermediate-dose arm (15%) received subsequent salvage HDC. At a median follow-up of 5 years, the intent-to-treat DFS was

Table 2. Randomized trials in high-risk primary breast cancer.

Trial (Chair)	*Population (# + nodes)*	*N*	*F-U*	*DFS HDC*	*DFS Control*	*p*	*OS HDC*	*OS Control*	*P*	*Status*
Netherlands, NWAST (Rodenhuis)[54]	≥4	885	First 284 pts 4.5 yrs	3-yr: 77%	3-yr: 62%	0.009	3-yr: 89%	3-yr: 79%	0.03	Preliminary analysis (5/00)
			Whole file 3.5 yrs	3-yr: 72%	3-yr: 65%	0.05	3-yr: 84%	3-yr: 80%	0.3	
USA, CALGB 9082 (Peters)[52]	≥10	785	5.1 yrs	61%	60%	0.49	70%	72%	0.23	Preliminary analysis (5/01)
Anglo-Celtic I (Leonard)[55]	≥4	605	First 100 pts >6yr	59%	43%	NR	NR	NR	NR	Preliminary analysis (5/02)
			Whole file 4 yr	51%	54%	0.6	63%	62%	0.8	
Scandinavia (Bergh)[53]	>5 to 8	525	34 mo	3-yr: 63%	3-yr: 72%	0.04	3-yr: 77%	3-yr: 83%	0.12	Preliminary analysis (5/99)
Italy, Michelangelo (Gianni)[59]	≥4	382	52 mo	5-yr: 65%	5-yr: 62%	NS	5-yr: 77%	5-yr: 76%	NS	Preliminary analysis (5/01)
France, PEGASE 01 (Roché)[58]	>7	314	33 mo	3-yr: 71%	3-yr: 55%	0.002	3-yr: 84%	3-yr: 85%	0.33	Preliminary analysis (5/01)
Germany (Zander)[57]	≥10	302	3.7 yrs	6-yr: 50%	6-yr: 25%	0.09	NR	NR		Preliminary analysis (5/02)
Japan, JCOG (Tokuda)[76]	≥10	95	4 yrs	60%	48%	0.4	67%	66%	0.9	Preliminary analysis (5/01)
Netherlands Cancer Institute (Rodenhuis)[48]	≥4	81	6.9 yrs	49%	47.5%	0.37	62.5%	61%	0.85	Final analysis
USA, MDACC (Hortobagyi)[49]	≥10+ or ≥4 after NAC	78	6.5 yrs	48%	62%	0.35	58%	77%	0.23	Final analysis
USA, SWOG 9623 (Bearman)	4-9	1,000	–	–	–	–	–	–	–	Accrual completed
USA, ECOG (Tallman)	≥10	550	–	–	–	–	–	–	–	Accrual completed
Australia, IBCSG Basser)	≥10	340	–	–	–	–	–	–	–	Accrual completed

NWAST: Netherlands Working Party on Autologous Solid Tumor Transplantation. CALGB: Cancer And Leukemia Group B. PEGASE: Programme d'Étude de la Greffe Autologue dans les Cancers du Sein. JCOG: Japan Clinical Oncology Group. MDACC: MD Anderson Cancer Center. SWOG: Southwest Oncology Group. ECOG: Eastern Collaborative Oncology Group. IBCSG: International Breast Cancer Study Group. NAC: neoadjuvant chemotherapy. NR: not reported. NS: not significant.

61% in the HDC arm and 60% in the ID arm (p=0.5). There were fewer relapses in the high-dose arm (32.2% [95% confidence interval, 27 to 37.8%]) than in the ID arm (42.7.1% [95% CI, 37.1 to 48.5%]), particularly in women younger than 50. This represents a 31% relative reduction in the frequency of relapses, which is certainly consistent with a dose-response effect. However, there were 32 toxic deaths (8.1%) in the HDC arm, versus none in the ID arm. Thus, the lower incidence of recurrences in the high-dose arm appeared offset by the high transplant-related mortality observed in this trial. No significant difference in OS was observed (70% vs. 72%, p=0.2). At current lead follow-up of 10 years, the OS in both arms is superior to any previous experience in CALGB or any other conventional chemotherapy study in this population. While the outcomes in the high-dose arm are as predicted from the pilot phase II study,[26,28] patients in the ID arm have fared much better than expected during the design of the trial. The reasons for this are unclear, and may include the clinical benefit from the addition of one cycle of G-CSF-supported ID chemotherapy at the end of treatment,

extensive pre-enrollment staging, or the confounding effect from salvage HDC.

Bergh *et al.* reported the first analysis of the Scandinavian trial, which enrolled patients with either ≥ 8 involved nodes, or ≥ 5 involved nodes with an ER negative and high S-phase fraction tumor.[53] Five hundred and twenty-five patients were randomized to receive nine cycles of individually tailored dose-intensive fluoruracil, epirubicin and cyclophosphamide (FEC), or three cycles of conventional FEC, followed by HDC. Doses in the tailored FEC arm were escalated to as high as 120 mg/m^2 of epirubicin and 1,800 mg/m^2 of cyclophosphamide per cycle, according to the blood nadir counts of the preceding cycle. None of the usual staging tests in HDC clinical trials was performed before randomization to exclude women with metastatic disease. The cumulative chemotherapy doses in the tailored dose-intensive arm significantly exceeded those in the HDC arm. At a median follow-up of 34 months, the DFS rates in the transplant and the tailored FEC arms were 65% vs. 72% (p=0.04), with respective OS rates of 77% and 83% (p=0.1). Despite the short follow-up, eight cases of secondary myelodysplastic syndrome/acute leukemia (3.2%) had already been noticed in the tailored FEC arm, and more cases are likely to be detected. Two patients in the transplant arm (0.7%) died from acute regimen-related toxicity. A major problem in interpreting this study is the fact that the *control* arm received doses well above those considered standard, as well as higher total cumulative doses than the *high-dose* arm. Neither this trial nor the CALGB study contained a control arm receiving a chemotherapy regimen that can be considered standard.

The largest randomized trial is the National Dutch study, which targeted patients with four or more positive axillary nodes. Rodenhuis and colleagues randomized 885 patients (570 with four to nine, and 315 with ten or more positive nodes) to receive, postoperatively, five cycles of FEC, or four cycles of FEC followed by HDC.[54] This trial was well designed, with a 90% power to detect a decrease in relapse hazard of 24%. Every bit as important, the conduction of this study was superb, with the following remarkable features: 1) low (1%) transplant-related mortality; 2) no patients randomized to the control arm went on to receive transplant off study; 3) low drop-out rate (6%) was observed in the transplant arm; and 4) truly population-based enrollment that is rarely seen in prospective interventional studies in medicine. At the time of its first preliminary analysis, only 200 of the expected 570 events had occurred. By requirement of the Dutch insurance agencies that funded the trial, a prospectively planned subset analysis of the first 284 enrolled patients was performed, after a median follow-up of 4.5 years. The transplant subset had superior DFS (77% vs. 62%, p=0.009) and OS (89% vs. 79%, p=0.04), in both the 4-9 and the ≥10 positive lymph node categories. Importantly, only during the fourth year of follow-up did the DFS and OS curves of both arms start to separate. In an early analysis of the whole study file after a median follow-up of 3.5 years, differences in DFS between the transplant and the control arm were of border-line significance (72% vs. 65%,p=0.05), with no differences in OS (84% vs. 80%, p=0.3).

Similar observations to those of the Dutch study were made in the first preliminary analyses of the Anglo-Celtic and the German studies. In the former trial, Crown *et al.* randomized 605 patients with four or more positive nodes to receive either HDC or maintenance CMF following four cycles of adriamycin.[55] At a median follow-up of 4 years, no differences were noted between the transplant arm and the control arm in the whole study file in terms of DFS (51% vs. 54%, p=0.6) or OS (63% vs. 62%, p=0.8). However, an unplanned evaluation of the first 100 patients enrolled, prompted by the subset observations of the Dutch study, revealed fairly large differences in favor of the transplant arm (59% vs. 43%).[56]

In the first analysis of the German trial enrolling patients with ten or more involved nodes, Zander *et al.* reported a substantial DFS advantage for the transplant arm in those patients with longest follow-up, with 6-year actuarial DFS rates of 50% and 25%, respectively.[57] No DFS or OS differences were noted for the whole study file of 302 patients at a median follow-up of 3.7 years.

Differences in DFS of similar magnitude to those seen in the subset analyses of those studies were reported in the first analysis of the French trial PEGASE 01 for patients with more than 7 involved lymph nodes. Roché *et al.* randomized 314 patients to receive standard adjuvant chemotherapy followed by HDC or observation.[58] The transplant-related mortality was 0.6%. At a short median follow-up of 33 months, there were statistically significant differences in DFS (71% vs. 55% p=0.002), but not in OS (84% vs. 85%, p=0.3).

Gianni *et al.*, at the National Cancer Institute in Milan, compared their high-dose sequential single-agent approach to conventional chemotherapy in 382 patients with four or more positive nodes.[59] The treatment-related mortality observed in the high-dose sequential arm was 0.5%. At a median follow-up of 52 months, no differences in DFS (65% vs. 62%) or OS (76% vs. 77%) were noted between the high-dose sequential and the control arms. A possible DFS advantage in favor of the high-dose arm was suggested in the subset of younger patients (as in the CALGB study), and in those with 4-9 positive nodes.

Considerations about the interpretation of the available results

Randomized trials adjust for known biases, and constitute the yardstick by which all new treatments are measured. However, the following issues should be considered when evaluating the capacity of an individual randomized trial to address a research question.

Size and statistical power. The randomized HDC studies for MBC are small, with the largest one, the Canadian, having randomized just over 220 patients. The adjuvant trials are of moderate size, at most. The limited size of these studies contrasts with the large accrual in phase III trials of conventional chemotherapy, in which enrollment of many hundreds or thousands of patients is the rule. In addition, some of the HDC trials are further limited by the drop-out in the high-dose arm, which is not uncommon in transplant studies. Obviously, the reliability of intent-to-treat analyses in the presence of large drop-out rates is questionable. Whether reduced sample sizes are caused by unrealistic expectations at the time of study design or by unforeseen difficulties in subsequent accrual, small trials can miss potentially important differences, and their results need to be interpreted with great caution. Meta-analyses, such as the one recently initiated by the European Bone Marrow Transplant Solid Tumor Working Group, will provide increased power to address this question.

Length of follow-up. The median time to relapse of HRPBC patients after standard chemotherapy is around two to three years. In contrast, the majority of relapses after HDC for HRPBC occur within that time period (Figure 2). Therefore, early analyses of the adjuvant studies will detect most of the relapses in the transplant arm, but only around half of the recurrences in the control arm. With respect to the survival analysis, interpretation of preliminary results needs to take into account that around half of all MBC patients survive at least two years with conventional management. Furthermore, in adjuvant trials another two years of median OS after metastatic recurrence should be factored in.

The inappropriateness of drawing conclusions after preliminary analyses of the randomized studies cannot be overemphasized. Numerous examples illustrate this point. Berry *et al*. retrospectively compared the OS of 635 MBC patients enrolled in CALGB trials of standard-dose chemotherapy with that of 441 MBC patients treated with HDC and registered at the American Bone Marrow Transplant Registry.[60] This analysis was restricted to patients younger than 65 who had responded to a single chemotherapy regimen in the metastatic setting, with both groups of patients being matched for known prognostic factors. No OS differences were observed during the first two years after treatment, and only after the third year of follow-up did significant differences emerge. The 3-year and 5-year OS rates in the HDC group (37% and 22%, respectively) were significantly superior to those in the standard-dose group (27% and 13%, respectively, p=0.01). The randomized Parma study for aggressive non-Hodgkin's lymphoma provides another good example of the importance of follow-up in transplant studies. Its preliminary analyses were negative,[61,62] and only after the appropriate duration of follow-up did statistically significant differences become apparent, with 5-year DFS rates of 46% and 12% for the HDC and control arms, respectively.[63] In the French randomized trial of autografting for myeloma, the curves did not start to separate until after three years of minimum follow-up, which did not prevent long-term differences from emerging in favor of transplant.[64]

Mature follow-up becomes more critical when the individual size of the trials is small. It is essential that the metastatic Canadian and PEGASE 03 trials be allowed to mature, before any meaningful conclusions regarding OS are made. Due to the different natural history of metastatic and non-metastatic disease, long-term follow-up becomes even more necessary in adjuvant studies. The subset analyses of the Dutch and the Anglo-Celtic study suggesting important DFS differences in those patients with longest follow-up are very provocative. Since there were no obvious demographic or prognostic differences between those first subsets and the rest of the study files, the difference in follow-up is the most likely explanation. In the PEGASE 01 trial, the fairly large DFS advantage already seen in favor of HDC, has, predictably, not translated yet into OS differences. We should by now have learnt the lesson that premature evaluation of randomized trials is often misleading.

The clinical benefit already observed in some of the studies should not be underrated. This point relates to the value of absolute versus relative improvements observed with a new treatment. Detection of statistically significant differences between two treatments does not imply that such differences are necessarily clinically relevant. A way of quantifying the clinical relevance is by calculating the number of patients needed to be treated to benefit one, which is expressed by the ratio *1/absolute* differences. Emphasizing the differences observed in a randomized trial in terms of relative risk decrease can be misleading. The adjuvant CALGB 9344 study evaluating the addition of taxol to adriamycin-based conventional therapy in node-positive patients illustrates this point. This trial detected an improvement in OS at 18 months from 95% to 97%. This very small absolute difference reached statistical significance due to the large sample size (3,170 patients). While it represented a 20% relative decrease in the risk of death, its clinical relevance appears much more modest, with

as many as fifty patients needed to be treated in order to benefit one.

Conversely, the clinical benefit stemming from the 10-20% absolute differences already observed in the preliminary analyses of some of the HDC studies would, if confirmed, be substantial. As illustrated in Table 3, that degree of benefit would be equivalent or superior to other interventions in oncology that have been hailed as major advances (and rightly so) and have changed the standard of care, and vastly superior to many other breakthrough results in other medical fields. Consequently, designing a randomized trial to detect a very large (e.g., 30%) absolute difference is simply unrealistic, for HDC or for any other new intervention in oncology, or in medicine, for that matter. In breast cancer, such magnitude of impact would probably only be caused by surgery of the primary tumor in stage I-II patients compared to no treatment at all. The benefit of adjuvant systemic treatment, one of the mainstays of medical oncology, is a 20-30% relative decrease in relapse, depending on the specific population, but substantially smaller in absolute terms, as estimated in the Oxford meta-analyses.

Extent to which the study results are consistent with accepted standards. This issue is routinely addressed in surgical and radiotherapeutic trials. Many prominent surgeons questioned the quality of the surgery performed in a well-known randomized trial testing neoadjuvant chemotherapy in locally advanced non-small-cell lung cancer,[65] in view of the apparently substandard results of the surgery-alone arm. Similarly, old randomized trials of radiation for breast cancer employed techniques that have since become obsolete, causing a degree of toxicity and mortality that is presently not experienced by patients treated in state-of-the-art radiation therapy facilities. In the case of HDC, procedure-related mortality is clearly associated with the experience of the transplanting team. The toxic death rates greater than 5% observed in some of the studies, are considered excessive by modern standards. Likewise, excessive delay in patients proceeding to transplant in some of the trials may have resulted in worse than expected outcomes.

In summary, the controversy about the efficacy of HDC for breast cancer remains far from settled. Furthermore, the debunking of the two fraudulent South African trials shifted much of the debate away from the scientific arena. This scandal triggered a barrage of negative reports in the lay press that markedly harmed patient enrollment in important trials, such as the SWOG 9623 study for patients with four to nine involved nodes, which had been declared of high priority by the National Cancer Institute, and was forced to close without reaching its target accrual.

Table 3. Relative and absolute improvements observed in some of the HDC randomized trials compared to those observed in other interventional studies that have changed the standard of care in oncology and other medical fields.

Intervention	*Relative risk reduction*	*p value*	*Absolute risk reduction*	*Number needed to treat**
HDC vs. conventional treatment First subset of the Dutch randomized trial (≥4+ nodes)[54]	39% (event)	0.009	15%	7
HDC vs. conventional treatment PEGASE 01 (>7+ nodes)[58]	35% (event)	0.002	16%	6
HDC vs. conventional treatment PEGASE 03 (MBC)[42]	19% (event at 2 years)	0.0002	17%	5
Adjuvant polychemotherapy vs. placebo for breast cancer (Oxford overview)[77]				
Younger than 50				
Node -	19% (relapse)	<0.00001	10%	10
Node +	32% (relapse)	<0.00001	15%	7
Older than 50				
Node -	9% (relapse)	0.0007	6%	17
Node +	12% (relapse)	<0.00001	5%	20
Adjuvant tamoxifen for 5 years vs. placebo for hormone-receptor positive breast cancer (Oxford overview)[77]				
Node -	19% (relapse)	<0.00001	15%	6
Node +	25% (relapse)	<0.00001	15%	6
Adjuvant anthracycline vs. non-anthracycline (Oxford overview)[61]	6% (relapse)	0.006	3%	33
Chemotherapy + rituximab vs. chemotherapy for diffuse large B-cell lymphoma[79]	33% (event) 18% (death)	<0.001 0.007	19% 13%	5 8
Pamidronate vs. placebo for breast cancer with osteolytic bone metastases[80]	20% (skeletal complications)	<0.001	13%	8
Beta-blockers vs. placebo after myocardial infarction[81]	17% (death)	0.00001	1%	91
Streptokinase vs. placebo after myocardial infarction[82]	18% (death)	0.0002	2%	43
Warfarin vs. placebo in patients with atrial fibrillation[83]	69% (emboli)	<0.00001	3%	31
Captopril vs. placebo in patients with left ventricular dysfunction after myocardial infarction[84]	19% (death)	0.01	5%	20

**Number of patients needed to be treated in order to benefit one.*

Moreover, as it has been pointed out,[66] relatively small improvements in a large group of patients may involve larger benefits in smaller subgroups. This point was well argued by Richard Peto with respect

to the overall reduction in breast cancer mortality in the past decade.[67] As a result of studies honing in on prognostic factors, we can now predict which MBC patients are most likely to achieve long-term remissions after HDC, such as those with oligometastatic disease or those in complete remission.[68,69] Similar prognostic analyses have given equally valuable information in the HRPBC population.[70-72] Future comparative trials could be designed focusing on the populations most likely to benefit from HDC.

There is a pressing need to improve HDC for breast cancer. It appears unlikely that first-generation high-dose regimens developed two decades ago would end up being the optimal stem-cell supported high-dose combinations. Some have objected to research efforts attempting to develop HDC further, based on a higher priority for molecular targeted therapies.[73] These promising novel treatments may certainly help to improve outcome when combined with chemotherapy, but they are unlikely to have a substantial impact alone. Trastuzumab and other biological agents could be easily administered after transplant, or, perhaps even integrated into the high-dose regimen,[74] with the goal of magnifying the synergistic effect that exists between cytotoxic and molecularly targeted agents. Independently of whether the superior tumor debulking capacity of HDC translates into an improved outcome or not, post-transplant minimal residual disease could provide an optimal scenario for testing novel therapies.

Let us keep in mind that the standard therapy results in MBC and HRPBC remain virtually unchanged after decades of attempts to refine chemotherapy combinations. In accordance with previous analyses of the status of this controversial issue,[75] high-dose chemotherapy remains too important an option to be prematurely and frivolously discarded after preliminary analyses of a portion of the data. We need to allow the studies to mature, and then let the data speak for itself. The jury remains out. We continue to await its verdict eagerly.

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