Biol Blood Marrow Transplant 20 (2014) 501–506

Adjuvant High-Dose Chemotherapy with Autologous Hematopoietic Stem Cell Support for High-Risk Primary Breast Cancer: Results from the Italian National Registry

Paolo Pedrazzoli [1], Giovanni Martinelli [2], Alessandro Massimo Gianni [3], Gian Antonio Da Prada [4], Alberto Ballestrero [5], Giovanni Rosti [6,†], Giovanni Luca Frassineti [7], Michele Aieta [8,‡], Simona Secondino [9,§], Saverio Cinieri [2,‖], Roberta Fedele [10], Carmelo Bengala [11,¶], Marco Bregni [12,#], Donatella Grasso [1], Ugo De Giorgi [7], Francesco Lanza [13], Luca Castagna [14], Barbara Bruno [15], Massimo Martino [10,*] on behalf of Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule staminali emopoietiche e terapia cellulare (GITMO) – Sezione Tumori Solidi

[1] *Medical Oncology, IRCCS Foundation, San Matteo Hospital, Pavia, Italy*
[2] *Medical Oncology, European Institute of Oncology, Milan, Italy*
[3] *Medical Oncology, IRCCS Foundation, National Cancer Institute, Milan, Italy*
[4] *Medical Oncology, IRCCS Maugeri Foundation, Pavia, Italy*
[5] *Department of Internal Medicine, University Hospital, Genova, Italy*
[6] *Medical Oncology, Civil Hospital, Ravenna, Italy*
[7] *Department of Medical Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy*
[8] *Medical Oncology, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy*
[9] *Medical Oncology, Niguarda Ca', Granda Hospital, Milan, Italy*
[10] *Hematology and Bone Marrow Transplant Unit, Azienda Ospedaliera "BMM", Reggio Calabria, Italy*
[11] *Medical Oncology, University Hospital, Pisa, Italy*
[12] *Hematology Unit, San Raffaele Scientific Institute, Milan, Italy*
[13] *Section of Hematology and Bone Marrow Transplant Unit, Cremona, Italy*
[14] *Hematology Unit, Humanitas Cancer Center, Rozzano, Milan, Italy*
[15] *National Registry GITMO & Data Managing, Ospedale San Martino, Genova, Italy*

Article history:
Received 15 October 2013
Accepted 23 December 2013

Key Words:
Autologous hematopoietic progenitor cell support
High-dose chemotherapy
High-risk breast cancer

A B S T R A C T

The efficacy of high-dose chemotherapy (HDC) and autologous hemopoietic progenitor cell transplantation (AHPCT) for breast cancer (BC) patients has been an area of intense controversy among the medical oncology community. The aim of this study was to assess toxicity and efficacy of this procedure in a large cohort of high-risk primary BC patients who underwent AHPCT in Italy. A total of 1183 patients receiving HDC for high-risk BC (HRBC) (>3 positive nodes) were identified in the Italian registry. The median age was 46 years, 62% of patients were premenopausal at treatment, 60.1% had endocrine-responsive tumors, and 20.7% had a human epidermal growth factor receptor 2 (HER2)–positive tumor. The median number of positive lymph nodes (LN) at surgery was 15, with 71.5% of patients having ≥ 10 positive nodes. Seventy-three percent received an alkylating agent-based HDC as a single procedure, whereas 27% received epirubicin or mitoxantrone-containing HDC, usually within a multitransplantation program. The source of stem cells was peripheral blood in the vast majority of patients. Transplantation-related mortality was .8%, whereas late cardiac and secondary tumor-related mortality were around 1%, overall. With a median follow-up of 79 months, median disease-free and overall survival (OS) in the entire population were 101 and 134 months, respectively. Subgroup analysis demonstrated that OS was significantly better in patients with endocrine-responsive tumors and in patients receiving multiple transplantation procedures. HER2 status did not affect survival probability. The size of the primary tumor and number of involved LN negatively affected OS. Adjuvant HDC with AHPCT has a low mortality rate and provides

Financial disclosure: See Acknowledgments on page 505.

* Correspondence and reprint requests: Dr. Massimo Martino, Hematology and Bone Marrow Transplant Unit, Department of Oncology and Hematology, Azienda Ospedaliera BMM, Via Cantaffio, 89133 Reggio Calabria, Italy.
E-mail address: dr.massimomartino@gmail.com (M. Martino).
† Current address: G. Rosti: Medical Oncology, S. Maria di Ca' Foncello Hospital, Treviso, Italy.
‡ Current address: M. Aieta: Medical Oncology, IRCCS-CROB, Rionero in Vulture (PZ), Italy.
§ Current address: S. Secondino: Medical Oncology, IRCCS Foundation, San Matteo Hospital, Pavia, Italy.
‖ Current address: S. Cinieri: Medical Oncology and Breast Unit, A. Perrino Hospital, Brindisi, Italy.
¶ Current address: C. Bengala: Medical Oncology, Misericordia Hospital, Grosseto, Italy.
# Current address: M. Bregni: Medical Oncology, di Circolo Hospital, Busto Arsizio, Italy.

1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2013.12.569

impressive long-term survival rates in patients with high-risk primary BC. Our results suggest that this treatment modality should be proposed in selected HRBC patients and further investigated in clinical trials.

INTRODUCTION

The clinical correlation between chemotherapy (CT) dose intensity, achieved either by increasing the single dose per cycle (ie, higher dose) or by reducing the intervals between cycles (ie, dose density), and outcome in breast cancer (BC) has been described since the 1980s [1,2]. This led, along with phase II studies apparently demonstrating significant favorable outcomes compared with historical data, to the premature acceptance of high-dose chemotherapy (HDC) with autologous hematopoietic progenitor cell transplantation (AHPCT) as a treatment option both in the adjuvant and metastatic settings, with up to nearly 2000 patients per year undergoing this procedure in the mid-1990s in Europe [3]. Unfortunately, the vast majority of patients were treated outside of prospective randomized studies.

At the turn of the century, in view of early reports of randomized trials not showing a significant overall survival (OS) benefit of HDC [4], the vast majority of medical oncologists no longer considered this procedure an option. In the era of great expectations for targeted drugs, data from randomized studies demonstrating an OS benefit of HDC for high-risk breast cancer (HRBC) [5,6], along with additional evidence of the benefit of intensified CT, did not change this attitude [7].

Recently, Berry et al. published the first meta-analysis using individual data from 15 trials for patients with HRBC, showing a significant benefit of HDC with AHPCT for disease-free survival (DFS) but not for OS [8]. The authors conclude that HDC with autologous support for patients with BC, as it was studied in these trials, does not produce sufficient benefit to be "worthwhile," despite an apparent improvement of OS confined to women with human epidermal growth factor receptor 2 (HER2)–negative disease, which is biologically plausible and supported by clinical data [6,9,10]. Based on the data of subgroup analyses and on the perspective of the new oncology aiming for individualized therapeutic strategies, some authors suggested that the clear-cut view of the meta-analysis is questionable, as HDC might be of potential benefit in selected patients, considering the present limited toxicity of the procedure [11-14].

As a contribution to this field, we report the results of this approach in a large cohort of patients treated in Italy between 1990 and 2005.

METHODS

The "Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule staminali emopoietiche e terapia cellulari" (GITMO) is an association established in 1987 with the purpose of designing and coordinating studies and collecting data from national and international (mainly via collaboration with the European Group for Blood and Marrow Transplantation) clinical research on patients undergoing autologous and allogeneic transplantation in Italy. GITMO centers, which are homogenously distributed through the country, are required to send patient data to the central European Group for Blood and Marrow Transplantation database on a yearly basis, either directly or through the GITMO itself. There are 2 levels of data: minimal essential data type A, which are compulsory and consider major items, such as demographic data, disease classification, type of transplantation, outcomes, and follow-up; and minimal essential data type B, referring to items sent on a volunteer basis (type of conditioning or mobilization regimens, complications, number of cells transplanted, etc).

Study Design and End Points

The purpose of the present study was to analyze the registry data on AHPCT performed in the adjuvant setting of HRBC (3 or more involved nodes, pN2) between 1990 and 2005. The primary outcome were DFS and OS; secondary end points were transplantation-related mortality (TRM), nonrelapse mortality (NRM), and identification of clinical and biologic features that may influence outcome of HDC. DFS and OS rates were measured from the date of transplantation to the date of last follow-up or death and the date of relapse, respectively. TRM was defined as mortality from any cause other than disease progression within 100 days of transplantation. NRM was defined as mortality from any cause other than disease progression and TRM after the transplantation.

Before starting the present analysis, GITMO centers were contacted for missing data.

Statistics

Probabilities of DFS, OS, and TRM were calculated using the Kaplan-Meier product limit estimate. The log-rank test was used for comparisons of DFS and survival between groups; stratifying parameters included menopausal status, age, hormone receptor status (estrogen- or progesterone-receptor positive versus both negative), HER2 status (positive versus negative), number of positive lymph nodes (LN), primary tumor (T) categories, and multiple versus single HDC.

RESULTS

Among 1352 patients reported in the registry, 1183 were available for OS analysis and represent the body of this paper. One hundred sixty-nine were excluded for incomplete data, erroneous reporting (ie, evidence of metastatic disease), or having <4 positive LN at surgery. The baseline patient and treatment characteristics are summarized in Table 1 and Table 2, respectively. The median age was 46 years (range, 28 to 66), and 62% of the women were premenopausal. Data on hormone receptor (HR) status and HER2 status were available in 1001 patients (85%) and 569 patients (48%), respectively. Triple negative (TN) disease was documented in 85 patients. Twenty six percent of patients had breast masses larger than 5 cm; the median lymph node involvement at surgery was 15 (range, 4 to 63); the number of patients having 4 to 9, 10 to 19, and $\geq$ 20 pathologic nodes was 337 (28.5%), 568 (48%), and 278 (23.5%), respectively.

Table 1
Patient Demographic and Clinical Characteristics

Characteristic	n	%
No. of patients	1183	100.0
Age, median (range), yr	46 (28-66)	
Menopausal status		
Premenopausal	734 (62.0)	62.0
Postmenopausal	449 (38.0)	38.0
Missing information	0	0
ER/PR status		
Negative	290 (24.5)	24.5
Positive	711 (60.1)	60.1
Missing information	182 (15.4)	15.4
HER2 status		
Negative	324 (27.4)	27.4
Positive	245 (20.7)	20.7
Missing information	614 (51.9)	51.9
Positive lymph nodes, median (range)	15 (4-63)	
4-9	337 (28.5)	28.5
10-19	568 (48.0)	48.0
≥20	278 (23.5)	23.5
Tumor size, cm		
≤5	875 (74.0)	74.0
>5	308 (26.0)	26.0

HER2 indicates human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.
Data shown are n (%) unless otherwise indicated.

Table 2
Treatment Characteristics

Characteristics of the treatments	Value
No. of cycles of conventional chemotherapy before AHPCT, median (range)	3 (0-6)
Containing anthracyclines	90
Containing taxanes/anthracyclines	33
Time from breast cancer diagnosis to transplantation, median (range), wk	14 (3-25)
Peripheral blood CD34+ cells	>95
Single AHPCT	80.1
Multi AHPCT	19.9
Conditioning treatment	
High-dose alkylating agents*	73
With adriamycin/epirubicin or mithoxantrone	27
Hormonal therapy after AHPCT	63

AHPCT indicates autologous hemopoietic progenitor cell transplantation.
Data are shown percentage (%) unless otherwise indicated.
* Either thiothepa or melphalan in 90% of cases.

Virtually all AHPCT were performed using mobilized peripheral blood HPC (>95%) and all patients received granulocyte colony-stimulating factor support after transplantation; 236 patients (19.9%) underwent the procedure more than once. The conditioning regimens included alkylating agents in 73% of cases, either thiothepa or melphalan (90%), and adriamycin/epirubicin or mitoxantrone were used in 27% of cases. In a few cases of T4 disease and N+ clinical involvement, a single high-dose procedure after conventional dose CT was performed before surgery as neoadjuvant therapy. Conventional anthracycline-based or, in more recent years, anthracycline/taxane-based adjuvant chemotherapy always preceded HDC, but only in the triple AHPCT setting [15]. Among patients with HR-positive tumors, the vast majority were treated with tamoxifen after HDC. Radiotherapy was administered after completion of CT, according with local recommendations.

Disease-free and Overall Survival Estimates

Kaplan-Meier curves of DFS and OS for the whole study population are shown in Figure 1A and B, respectively. With a median follow-up of 7.1 years, the DFS was 9.6 years, with 65% of patients free of disease at 5 years, whereas median OS was not reached, with 75% of the patients alive 5 years after transplantation.

Menopausal status (Figure 2A) and age < 50 versus ≥ 50 years did not affect survival. We found that survival was statistically better for patients with HR-positive and smaller (T1 to T2) tumors (Figure 2B and C). In our series, HER2 status did not affect survival. TN patients performed well with AHPCT (median OS, 110 months or 9.2 yrs), although outcome, as expected, was worse compared with the whole population.

Patients with 4 to 9 positive axillary nodes had 85% survival probability at 5 years; this result decreasing approximately by 10% for patients with 10 to 19 positive nodes and by a further 10% for patients with 20 or more positive nodes (Figure 2D).

Patients who underwent multiple HDC had a superior DFS and OS (Figure 3A) compared with single HDC, not reaching the median yet in both parameters, with 75% of them still alive and disease free 7.5 years after transplantation. This favorable effect was more clearly observed in patients with >9 positive LN (Figure 3B).

Toxicity and Secondary Malignancies

Because of the limited information provided by the minimal essential data type A form, detailed information on acute and long-term morbidity, including grade of mucositis and occurrence of infection, cannot be provided.

Treatment-induced menopause, defined as >2 years of amenorrhea after HDC with no resumption of menses, was found in a large proportion of patients who were premenopausal at the time of diagnosis.

Neutrophil and platelet recovery occurred in all but 4 patients who died before engraftment for infections. Overall TRM occurred in 9 of 1183 (.8%); NRM was negligible (16 of 1183, 1.4%) and this consisted of heart failure (2 of 1183, 0.2%) or second neoplasia (14 of 1183, 1.2%). Most second malignancies were gynecologic and there was a single case of acute leukemia.

DISCUSSION

The present study, reporting a retrospective analysis of data on HDC and AHPCT for HRBC in Italy, includes 1 of the largest series (1183 patients) in this setting. Despite that, we are aware of its limitations inherent to the retrospective study design, which selects patients on the basis of pathologic staging and those who have successfully achieved both surgery and HDC with AHPCT, and it excludes those that do not. Also, nonstandard pretreatment staging might have been used in some centers.

The patient population subject of the present analysis was selected to have at least 4 positive LN. Selection based on axillary node involvement was adopted by all phase III studies of HDC [8], as it was considered (and it is still today) a major negative prognostic factor for recurrence. In our study, patients with more than 10 pathologic nodes were the majority, and almost one quarter of our patients had more than 20 positive LN. Other patient characteristics, such as age and premenopausal state, were in line with previous studies [5,15-19]. Based on these considerations, the present population has clinical features and risk of BC recurrence and

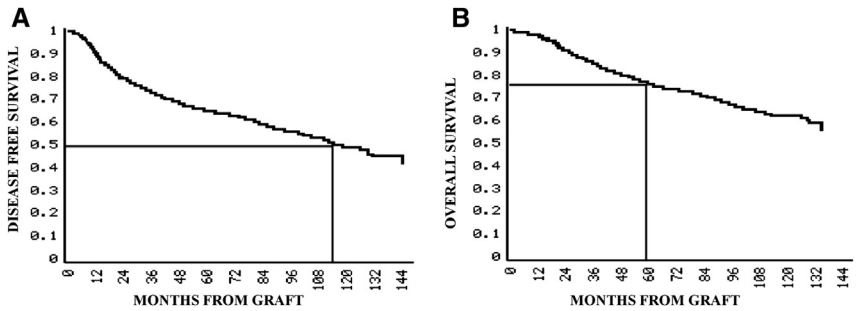

Figure 1. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival for the whole study population.

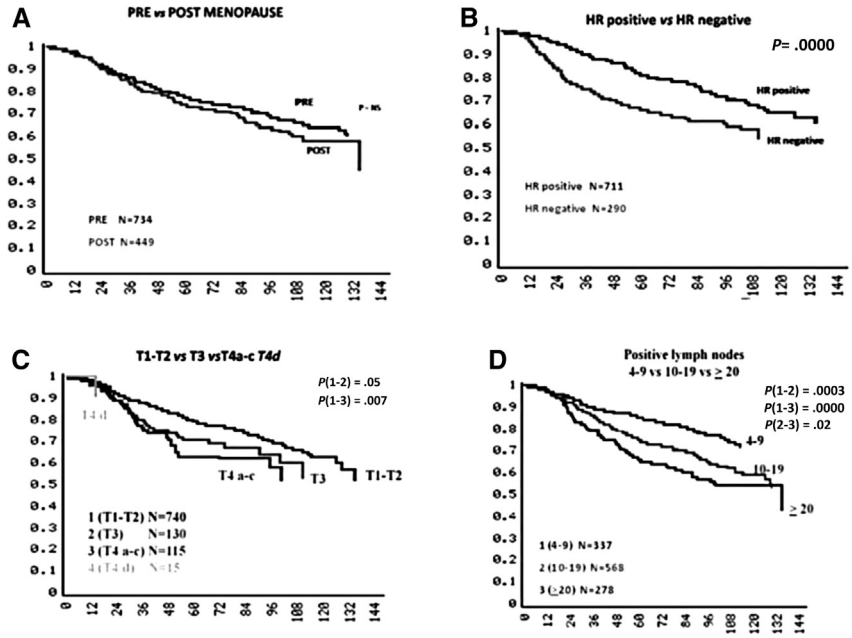

Figure 2. Kaplan-Meier estimates of overall survival in prespecified subset analyses. Subsets by (A) menopausal status, (B) tumor hormone-receptor status, (C) tumor size, and (D) number of positive lymph nodes. Survival is calculated in months from time of transplantation.

death that, with opportune caution, are likely to be similar to previous series. Unfortunately, data regarding patterns of recurrence and salvage therapy were not available, which represents a limitation of our study.

The data presented here revealed a very low toxicity of this approach, in terms of TRM, with death rates that are comparable with those of conventional CT. This is particularly significant considering that 20% of patients underwent multiple cycles of HDC. The introduction of myeloid growth factors after transplantation, the use of blood in place of bone marrow stem cells, and other improvements in supportive care reduced the TRM rate from the initial unacceptable 4% to 10% rate [20,21] to the current <1% expected in experienced transplantation units [22,23]. Thus, HDC has become substantially less toxic over time and today it should be considered a safe procedure [3,5] with a mortality rate and quality-adjusted survival parameters [24], similar to conventional CT. In addition, HDC regimens associated with a high TRM, ie, the cyclophosphamide/BCNU/cisplatin regimen [20], are no longer utilized and were only anecdotally used in our series.

Long-term toxicity was also not relevant. Gynecologic malignancies were prevalent among second tumors and might well be related to the presence of germline mutations of *BRCA* genes (ovarian cancer) or the use of adjuvant tamoxifen (uterine cancer). Heart failure was merely occasional, as was secondary acute leukemia, which occurred only in 1 case.

The survival benefit from HDC, which in our series appear to match favorably with previous adjuvant studies in similar patient population [25,26], was observed independently of age and menopausal state. No interference of the menopausal state was observed, possibly because a higher proportion of premenopausal women at the time of HDC became persistently amenorrheic after the procedure [5].

The impact of prognostic factors for survival, such as HR positivity, was maintained. Positivity for HR is a known positive prognostic factor, characterized usually by more indolent disease, and allows for hormonal targeted therapy after recovery from HDC, an opportunity that may have further influenced these results. Improved outcomes for HR-positive versus HR-negative disease is a recurrent feature in

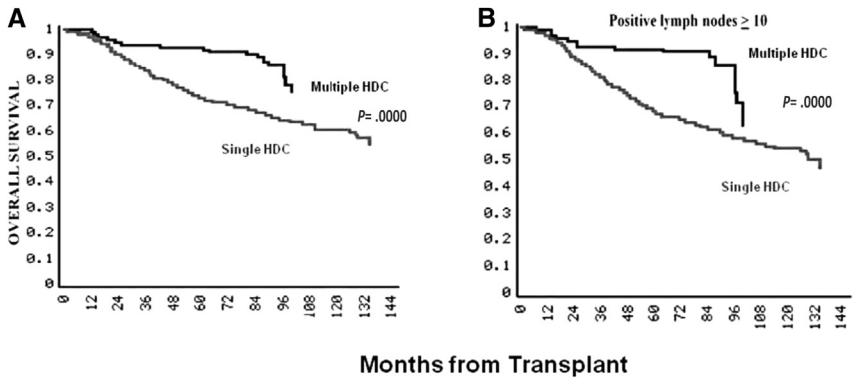

Figure 3. Kaplan-Meier estimates of overall survival. Comparison of multiple versus single high-dose chemotherapy (HDC) and autologous transplantation procedures. (A) Shows the whole study population. (B) Shows patients with ≥ 10 positive lymph nodes.

some HDC series [5], but not others [21], and one study pointed out that women with HR-positive disease had the most evident benefit from HDC [15]. HER2 status did not affect DFS and OS in our series, in contrast with previous reports [11]. This is likely to be related to the fact that 48.1% of patients had HER2 status available, so the analysis was conducted in a limited portion of our patients. The study by Rodenhuis et al. [6] underscored a difference in terms of DFS and OS in favor of the HER2-negative population, and discussed this finding in terms of insufficient anthracycline exposure for patients harboring HER2-positive tumors (a population likely to benefit most from full-dose anthracyclines). The vast majority of HDC regimens used in their study did not include anthracycline in the conditioning regimen. One can hypothesize that the different results reported in our studies may be related to the significant number of HDC regimens containing anthracyclines (27%), and/or the introduction of anti-HER2 drugs in the adjuvant or metastatic phase.

Unfortunately, TN disease was documented in only 85 patients, so the apparent good results obtained this population are insufficient to generate any hypothesis. However, Gluz et al. [27] found that the benefit of HDC was more evident in a basal-like phenotype (ER and PR receptor negative, HER2-negative and basal cytokeratin positive) and in grade 3 tumors. Berry's meta-analysis [8] added to the body of evidence supporting a possible survival advantage for dose-intensification regimens for TN tumors. Other authors have speculated that these patients are the most likely to receive a benefit from HDC [28].

As with other treatment modalities, TN status had an impact on the HDC outcome, both in DFS and OS, which underscores the quality of the GITMO data. Highly significant differences in OS are noted if patients are stratified into 3 groups: 4 to 9, 10 to 19, and more than 20 positive nodes. In the Rodenhuis study [16], including patients with >3 positive nodes, the most relevant effect of HDC compared with conventional CT was observed in terms of DFS in the group having more than 9 positive LN.

An interesting trend emerging from our study was the impact of multiple, less intensive, cycles of HDC versus single, more intense HDC. Overall, the dose intensity might be superior in the multiple transplantation approach, thus justifying the better outcome observed in our study and suggested by previous studies [11]. The strategy consisting of rapidly cycled HDC courses could be considered mainly for theoretical reasons and clinical trials. On the basis of kinetic models, some authors discussed early intensification strategies to avoid gradual expansion of clinically not apparent pre-existing subclones of cells that are resistant to the induction regimen and are hidden by the simultaneous regression of numerically dominant sensitive clones [29]. As a matter of fact, the best results of HDC in HRBC were obtained by the German study, including a double-HDC approach, which was compared with an appropriate dose-dense conventional CT [5]. A such "high dose–density" strategy may increase the intensity of anticancer therapy beyond that achievable with conventional, dense-dose, or with single HDC [5,6,15,19,30,31]. Cost savings associated with outpatient-based AHPCT, feasible in BC patients undergoing less intensive HDC regimens, are also relevant [32,33].

In conclusion, our study, along with some more recent phase III studies [5,6] and, to some extent, the results from meta-analysis [8,11], suggest a role for HDC and AHPCT in the context of HRBC, especially in view of the fact that this procedure can now be given safely and with the needed dose intensification, with both early and late minimal toxicity. In the adjuvant setting of HRBC, HDC with AHSCT may still represent a therapeutic option that can be proposed to well-informed patients harboring HER2-negative tumors and having gross involvement of axillary nodes. In recent years, new biologic factors have been reported to identify patients with high-risk primary BC who could benefit from modern dose-intensification regimens [10], and further studies should be conducted comparing conventional CT with high-dose strategies in the setting of HRBC, including locally advanced and inflammatory disease.

ACKNOWLEDGMENTS

The authors thank all Italian Centers that gathered all relevant information to locate eligible patients and performed data management: Milan (European Institute of Oncology: F. Peccatori), Genova (University of Genova: R. Gonella, F. Patrone), Ravenna (M. Marangolo), Meldola - Forli' (D. Amadori, N. Giovannini), S.Giovanni Rotondo (E. Maiello), Milan (Niguarda Hospital: S. Siena, R. Schiavo), Pavia (IRCCS San Matteo University Hospital Foundation: M. Danova), Firenze (A. Bosi and S. Guidi), Modena (F. Narni and R. Sabbatini), Cagliari (E. Angelucci), Reggio Calabria (P. Iacopino, F. Morabito, G. Messina, and G. Irrera), Udine (R. Fanin and F. Patriarca), Perugia (L. Crino' and M.A. Colozza), Bologna (S.Orsola Hospital: A. Martoni, and C. Zamagni), Milan (Humanitas Cancer Center: A. Santoro), Candiolo (M. Aglietta and A. Capaldi), Milan (San Raffaele: F. Ciceri), Noale (O. Vinante), Palermo (M. Musso and F. Porretto), Verona (G.L. Cetto and L. Battistelli), Reggio Emilia (L. Gugliotta and A. Bonini), and Pisa (P.F. Conte and V. Guarneri).

Authorship statement: Study concepts by P.P., C.B., G.R., M.B., and M.M. Data acquisition by P.P., B.B., S.S., and M.M.. Quality control of data and algorithms by P.P., B.B., and M.M.. Data analysis and interpretation by P.P., B.B., and M.M.. Statistical analysis by P.P. and B.B.. Manuscript preparation by P.P., D.G., R.F., M.B., U.D.G., and M.M.. Manuscript editing by P.P., D.G., R.F., and M.M.. Manuscript review by P.P., G.M., A.M.G., G.A.D., A.B., G.R., G.L.F., M.A., S.S., S.C., R.F., C.B., M.B., D.G., U.D.G., F.L., L.C., B.B., and M.M..

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *J Clin Oncol*. 1986;4:1162-1170.
2. Bonadonna G, Valagussa P, Tancini G, et al. Current status of Milan adjuvant chemotherapy trials for node-positive and node-negative breast cancer. *NCI Monogr*. 1986;(1):45-49.
3. Pedrazzoli P, Ferrante P, Kulekci A, et al. Autologous hematopoietic stem cell transplantation for breast cancer in Europe: critical evaluation of data from the European Group for Blood and Marrow Transplantation (EBMT) Registry 1990-1999. *Bone Marrow Transplant*. 2003;32:489-494.
4. Pedrazzoli P, Rosti G, Secondino S, et al. High-dose chemotherapy with autologous hematopoietic stem cell support for solid tumors in adults. *Semin Hematol*. 2007;44:286-295.
5. Nitz UA, Mohrmann S, Fischer J, et al. Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral-blood stem-cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a multicentre Phase III trial. *Lancet*. 2005;366:1935-1944.
6. Rodenhuis S, Bontenbal M, van Hoesel QG, et al. Efficacy of high-dose alkylating chemotherapy in HER2/neu-negative breast cancer. *Ann Oncol*. 2006;17:588-596.
7. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide

compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clini Oncol*. 2010;28:2874-2880.
8. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. *J Clin Oncol*. 2011;29:3214-3223.
9. Nieto Y, Shpall EJ. High-dose chemotherapy for high-risk primary and metastatic breast cancer: is another look warranted? *Curr Opin Oncol*. 2009;21:150-157.
10. Gluz O, Mengele K, Schmitt M, et al. Y-box-binding protein YB-1 identifies high-risk patients with primary breast cancer benefiting from rapidly cycled tandem high-dose adjuvant chemotherapy. *J Clin Oncol*. 2009;27:6144-6151.
11. Martino M, Bottini A, Rosti G, et al. Critical issues on high-dose chemotherapy with autologous hematopoietic progenitor cell transplantation in breast cancer patients. *Expert Opin Biol Ther*. 2012;12:1505-1515.
12. De Giorgi U, Amadori D. Dose intensification in hormone receptor-negative and/or human epidermal growth factor receptor 2-negative high-risk primary breast cancer. *J Clin Oncol*. 2012;30:758.
13. Moroni M. High-dose chemotherapy as adjuvant therapy in breast cancer: could there be a survival benefit? *J Clin Oncol*. 2012;30:759.
14. Wang J, Zhang Q, Zhou R, et al. High-dose chemotherapy followed by autologous stem cell transplantation as a first-line therapy for high-risk primary breast cancer: a meta-analysis. *PLoS One*. 2012;7:e33388.
15. Basser RL, O'Neill A, Martinelli G, et al. Multicycle dose-intensive chemotherapy for women with high-risk primary breast cancer: results of International Breast Cancer Study Group Trial 15-95. *J Clin Oncol*. 2006;24:370-378.
16. Rodenhuis S, Bontenbal M, Beex LV, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. *N Engl J Med*. 2003;349:7-16.
17. Moore HC, Green SJ, Gralow JR, et al. Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest Oncology Group/Intergroup study 9623. *J Clin Oncol*. 2007;25:1677-1682.
18. Gianni AM, Siena S, Bregni M, et al. Efficacy, toxicity, and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary nodes: five-year results. *J Clin Oncol*. 1997;15:2312-2321.
19. Peters WP, Rosner GL, Vredenburgh JJ, et al. Prospective, randomized comparison of high-dose chemotherapy with stem-cell support versus intermediate-dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114, and NCIC MA-13. *J Clin Oncol*. 2005;23:2191-2200.
20. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol*. 1993;11:1132-1143.
21. Tallman MS, Gray R, Robert NJ, et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. *N Engl J Med*. 2003;349:17-26.
22. Antman KH, Rowlings PA, Vaughan WP, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol*. 1997;15:1870-1879.
23. Damon LE, Hu WW, Stockerl-Goldstein KE, et al. High-dose chemotherapy and hematopoietic stem cell rescue for breast cancer: experience in California. *Biol Blood Marrow Transplant*. 2000;6:496-505.
24. Marino P, Roché H, Moatti JP. High-dose chemotherapy for patients with high-risk breast cancer: a clinical and economic assessment using a quality-adjusted survival analysis. *Am J Clin Oncol*. 2008;31:117-124.
25. Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. *JAMA*. 1995;273:542-547.
26. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*. 2005;352:2302-2313.
27. Gluz O, Nitz UA, Harbeck N, et al. Triple-negative high-risk breast cancer derives particular benefit from dose intensification of adjuvant chemotherapy: results of the WSG AM-01 trial. *Ann Oncol*. 2008;19:861-870.
28. De Giorgi U, Rosti G, Frassineti L, et al. High-dose chemotherapy for triple negative breast cancer. *Ann Oncol*. 2007;18:202-203.
29. Crown J, Wassherheit C, Hakes T, et al. Rapid delivery of multiple high-dose chemotherapy courses with granulocyte colony-stimulating factor and peripheral blood-derived hematopoietic progenitor cells. *J Natl Cancer Inst*. 1992;84:1935-1936.
30. Roche H, Viens P, Biron P, et al. High-dose chemotherapy for breast cancer: The French PEGASE experience. *Cancer Control*. 2003;10:42-47.
31. Tokuda Y, Tajima T, Narabayashi M, et al. Phase III study to evaluate the use of high-dose chemotherapy as consolidation of treatment for high-risk postoperative breast cancer: Japan Clinical Oncology Group study, JCOG 9208. *Cancer Sci*. 2008;99:145-151.
32. Martino M, Montanari M, Bruno B, et al. Autologous hematopoietic progenitor cell transplantation for multiple myeloma through an outpatient program. *Expert Opin Biol Ther*. 2012;12:1449-1462.
33. Meisenberg BR, Ferran K, Hollenbach K, et al. Reduced charges and costs associated with outpatient autologous stem cell transplantation. *Bone Marrow Transplant*. 1998;21:927-932.