Biol Blood Marrow Transplant 22 (2016) 475–481

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation as Adjuvant Treatment in High-Risk Breast Cancer: Data from the European Group for Blood and Marrow Transplantation Registry

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Article history:
Received 18 November 2015
Accepted 17 December 2015

Key Words:
Autologous hematopoietic stem cell transplantation
High-dose chemotherapy
High-risk breast cancer

A B S T R A C T

The aim of this retrospective study was to assess toxicity and efficacy of adjuvant high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (AHSCT) in 583 high-risk breast cancer (BC) patients (>3 positive nodes) who were transplanted between 1995 and 2005 in Europe. All patients received surgery before transplant, and 55 patients (9.5%) received neoadjuvant treatment before surgery. Median age was 47.1 years, 57.3% of patients were premenopausal at treatment, 56.5% had endocrine-responsive tumors, 19.5% had a human epidermal growth factor receptor 2 (HER2)-negative tumor, and 72.4% had ≥10 positive lymph nodes at surgery. Seventy-nine percent received a single HDC procedure. Overall transplant-related mortality was 1.9%, at .9% between 2001 and 2005, whereas secondary tumor-related mortality was .9%. With a median follow-up of 120 months, overall survival and disease-free survival rates at 5 and 10 years in the whole population were 75% and 64% and 58% and 44%, respectively. Subgroup analysis demonstrated that rates of overall survival were significantly better in patients with endocrine-responsive tumors, <10 positive lymph nodes, and smaller tumor size. HER2 status did not affect survival probability. Adjuvant HDC with AHSCT has a low mortality rate and provides impressive long-term survival rates in patients with high-risk BC. Our results suggest that this treatment modality should be considered in selected high-risk BC patients and further investigated in clinical trials.

Financial disclosure: See Acknowledgments on page 480.
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http://dx.doi.org/10.1016/j.bbmt.2015.12.011
1083-8791/

INTRODUCTION

The efficacy of high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (AHSCT) for breast cancer (BC) has been an area of intense controversy among the medical oncology community [1-3]. Several phase II studies, conducted throughout the 1980s and early 1990s, suggested that this approach improved long-term disease control [4-6]. This created great expectations among physicians and their patients, and HDC with AHSCT became widely used as a therapeutic option for BC [6]. However, in the early 2000s, due to preliminary reports from randomized studies failing to show improved overall survival (OS) benefit of HDC and a case of scientific misconduct [7], the scene was prematurely set for the demise of HDC in BC [8]. Consequently, the publication of randomized studies demonstrating an OS benefit by HDC has gone almost unnoticed in the oncology community [9,10].

In 2011 Berry et al. [11] reported a meta-analysis using data from randomized trials of HDC with AHSCT in high-risk BC patients. Of 6210 patients who participated in the 15 trials, HDC achieved a significant 13% reduction in the risk of recurrence, but this did not translate into a significant OS benefit despite an apparent improvement of OS in women with human epidermal growth factor receptor 2 (HER2)-negative disease, which is biologically plausible and supported by clinical data. Meta-analyses have been criticized as blunt instruments, compared with subgroup analyses and individualized therapeutic strategies, by some authors who suggest that HDC might be of potential benefit in subgroups of patients, considering the present limited toxicity of the procedure [1,3,12-14]. As a contribution to this field, we report the results of this approach in a large cohort of patients treated in Europe between 1995 and 2005.

METHODS

The European Group for Blood and Marrow Transplantation (EBMT) (www.ebmt.org) is a nonprofit organization established in 1974 to allow scientists and physicians involved in clinical SCT to share their experience and develop cooperative studies. The EBMT is divided into working parties, whose mission is the implementation of EBMT scientific and educational policy, the development and management of scientific proposals with the support of the Data Offices, the development and organization of educational activities with the support of the Executive Office, and assisting the development of definition of guidelines and policies. The Solid Tumor Working Party is dedicated to preclinical, translational, and clinical studies of cell therapy for solid tumors, including AHSCT and allogeneic HSCT, active and adoptive immunotherapy, and lymphoablative therapy with expanded T cells [15,16].

EBMT centers, which are homogenously distributed through European countries, are required to send patient data to the central EBMT database on a yearly basis. There are 2 levels of data: minimal essential data type A, which are compulsory and considered 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

The purpose of the present study was to analyze the EBMT registry data on primary, operable, nonmetastatic BC patients with 4 or more involved nodes at surgery who received HDC and AHSCT between 1995 and 2005 in Europe. The primary outcomes were disease-free survival (DFS) and OS; secondary endpoints were transplantation-related mortality (TRM), nonrelapse mortality (NRM), and identification of clinical and biological features that may influence outcome of HDC.

STATISTICS

Probabilities for DFS, OS, and TRM were calculated using the Kaplan-Meier product limit estimate. The log-rank (also called the Mantel-Cox test) and the Gehan-Breslow-Wilcoxon tests were used for comparisons of DFS and OS between groups [17,18]; stratifying parameters included menopausal status, age, hormone receptor (HR) status (estrogen or progesterone receptor positive versus both negative), HER2 status (positive versus negative), number of positive lymph nodes, primary tumor categories, and multiple versus single HDC. The log-rank test is the more powerful of the 2 tests if the assumption of proportional hazards is true. Proportional hazards means that the ratio of hazard functions (deaths per time) is the same at all time points. The Gehan-Breslow-Wilcoxon method gives more weight to deaths at early time points.

DFS and OS rates were measured from the date of surgery 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 365 days of transplantation. NRM was defined as mortality from any cause other than disease progression or TRM, after the transplantation. Before starting the present analysis, EBMT centers were contacted for missing data.

All P values were 2-sided, and a $P < .05$ was considered statistically significant. Statistical calculations were carried out by using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Among adjuvant patients with BC reported in the EBMT registry, 583 patients with 4 or more involved nodes at surgery were available for OS analysis and represent the body of this article. Informed consent to collect and register data to the EBMT record was obtained from participants. The baseline patient and treatment characteristics are summarized in Table 1. The median patient age was 47.1 years (range, 22.4 to 66.5), and 57.3% of women were premenopausal. Data on HR status and HER2 status were available in 84.7% and 31.4% of patients, respectively. Information for defining triple-negative (TN) BC (ie, tumors that lack estrogen receptor, progesterone receptor, and HER2 overexpression) was available in only 35 patients. Approximately 18% of patients had breast masses larger than 5 cm. The median number of lymph nodes involved at surgery was 13 (range, 4 to 46), and the number of patients having 4 to 9, 10 to 19, and >20 pathologic nodes was 27.6%, 52.4%, and 20%, respectively.

Virtually all AHSCTs were performed using mobilized peripheral blood hematopoietic progenitor cells (>95%). All patients received granulocyte colony-stimulating factor support after transplantation; 20.8% underwent HDC more than once.

The conditioning regimens included only alkylating agents in 73% of cases, whereas anthracyclines or mitoxantrone were used in 27% of cases. Either thiotepa of melphalan were included in most conditioning regimens.

In 55 patients (9.5%) harboring T4 disease (tumor of any size with direct extension to the chest wall and/or to the skin) and/or node-postitve clinical involvement (metastases to movable ipsilateral level I, II axillary lymph node(s) at presentation), a single HDC after conventional-dose chemotherapy was performed before surgery as neoadjuvant therapy. Conventional anthracycline-based or, in more recent years, anthracycline/taxane-based adjuvant chemotherapy always preceded HDC. Among patients with HR-positive tumors, most received tamoxifen after HDC. Radiotherapy was administered after completion of chemotherapy, in accordance with local recommendations.

Table 1
Patient Demographic, Clinical, and Treatment Characteristics

Characteristic	No. Patients (N = 586)	Percent
Median age, yr (range)	47.1 (22.4-66.5)	
<40	138	23.6
40-50	241	41.1
>50	207	35.3
Menopausal status		
Premenopausal	336	57.3
Postmenopausal	181	31.0
Missing information	69	11.7
HR status		
Negative	165	28.2
Positive	331	56.5
Missing information	90	15.3
HER2 status		
Negative	114	19.5
Positive	70	11.9
Missing information	402	68.6
Positive lymph nodes		
4-9	162	27.6
10-19	307	52.4
≥20	117	20.0
Tumor size, cm		
<2	134	22.9
2-5	295	50.3
>5	102	17.4
Missing information	55	9.4
Grading		
1-2	173	35.6
3-4	283	42.3
Missing information	130	22.1
Median no. of cycles of conventional chemotherapy before AHSCT (range)		4 (0-10)
Containing anthracyclines		84.1
Containing taxanes/anthracyclines		25.0
Neoadjuvant therapy		9.3
AHSCT with peripheral blood as source of stem cells		>95
Single AHSCT		79.2
Multiple AHSCT		20.8
Conditioning regimen		
Alkylating agents only		73
Including anthracyclines or mitoxantrone		27

DFS and OS Estimates

Kaplan-Meier curves of DFS and OS for the whole study population are shown in Figure 1A and B. With a median follow-up of 10 years, DFS was 7.2 years, with 64% and 44% of patients free of disease at 5 and 10 years, respectively. Median OS was not reached, with 75% and 58% of the patients alive 5 and 10 years after transplantation. Age (<40 versus >40 to 50 versus >50 years) (Figure 2A), menopausal status (Figure 2B), and single versus multiple HDC did not affect survival.

We found that survival was statistically better for patients with smaller size (<2 cm, 5-year survival probability of 78% and 10-year survival probability of 69%) as compared with those with sizes ranging from 2 to 5 cm (5-year survival probability of 73% and 10-year survival probability of 57%) and size > 5 cm (5-year survival probability of 63% and 10-year survival probability of 50%) (log rank test $P = .04$; Breslow test $P = .02$) (Figure 3A). Similarly, the cumulative survival was better in patients with tumor grading 1 to 2 (5-year survival probability of 79% and 10-year survival probability of 59%) compared with those with grade 3.4 (5-year survival probability of 65% and 10-year survival probability of 55%) (log rank test $P = .068$; Breslow test $P = .010$) (Figure 3B). The cumulative survival at 5 and 10 years was 78% and 61% in patients with HR-positive tumor and 64% and 55% in patients with HR-negative tumor, respectively (log rank test $P = .04$; Breslow test $P = .01$) (Figure 4).

Patients with 4 to 9 positive axillary nodes had 84% and 66% survival probability at 5 and 10 years, respectively. These figures decreased approximately by 10% for patients with 10 to 19 positive nodes and by a further 10% for patients with 20 or more positive nodes (log rank test $P = .0007$; Breslow test $P = .0004$; Figure 5). In patients harboring TN tumors, rates of DFS and OS at 5 and 10 years were 51% and 37% and 60% and 52%, respectively.

In a multiple Cox regression model including HR status, number of positive lymph nodes, and tumor size, only number of positive lymph nodes maintained an independent relationship with mortality (hazard ratio, 1.76; 95% confidence interval, 1.20 to 2.60; $P = .004$). The other 2 remaining variables were not significant ($P = .11$ to $.18$).

Toxicity and Secondary Malignancies

Because of the limited information provided by the minimal essential data type A form, detailed information on acute 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 reported in a large proportion of patients who were premenopausal at the time of diagnosis. Neutrophil and platelet recovery occurred in all but 5 patients who died before engraftment from infections. Overall TRM occurred in 11 of 583 cases (1.9%), at .9% between 2001 and 2005. Ten patients died in the first 100 days post-transplantation, and 1 patient with inactive hepatitis B died 8 months after transplantation from an abrupt increase in hepatitis B virus replication. NRM was 2.9% (17/583) and consisted of heart failure (5/583, .9%), on-road traffic accidents (2/583, .3%), suicide (1/583, .2%), unknown causes (4/583, .6%), and second neoplasia (5/583, .9% [4 solid tumors and 1 acute leukemia]).

DISCUSSION

The present study, reporting a retrospective data analysis on HDC and AHSCT for high-risk BC in Europe, includes 1 of the largest series in this field. Because it comes from a registry and derives from patients transplanted in many cases when only limited information on tumor biology was available, many parameters are lacking, making interpretation of results more difficult [19,20].

Patients included in the present analysis were selected if they had at least 4 positive lymph nodes. In the absence of other factors, mainly HER2 status, axillary node involvement was the major negative prognostic factor for recurrence [11] and was thus used to identify patients at high risk of recurrence to be selected for studies in the adjuvant setting.

Our results showed that adjuvant HDC with AHSCT, in contrast with early studies [21,22], is a safe procedure with a TRM that is, in more recent years, inferior to 1%. This is consistent with what has been observed in modern prospective studies [9,10]. Furthermore, in keeping with previous reports [11,19,20], the long-term effects of HDC do not differ from those observed with conventional chemotherapy, in particular regarding the risk of secondary cancer [11,23,24].

Survival rates in our study appear to be impressive when considering that all patients, including patients who received primary chemotherapy, had >3 positive nodes at surgery. Importantly, patients with more than 9 pathologic nodes were the vast majority (72.4%); this population has an

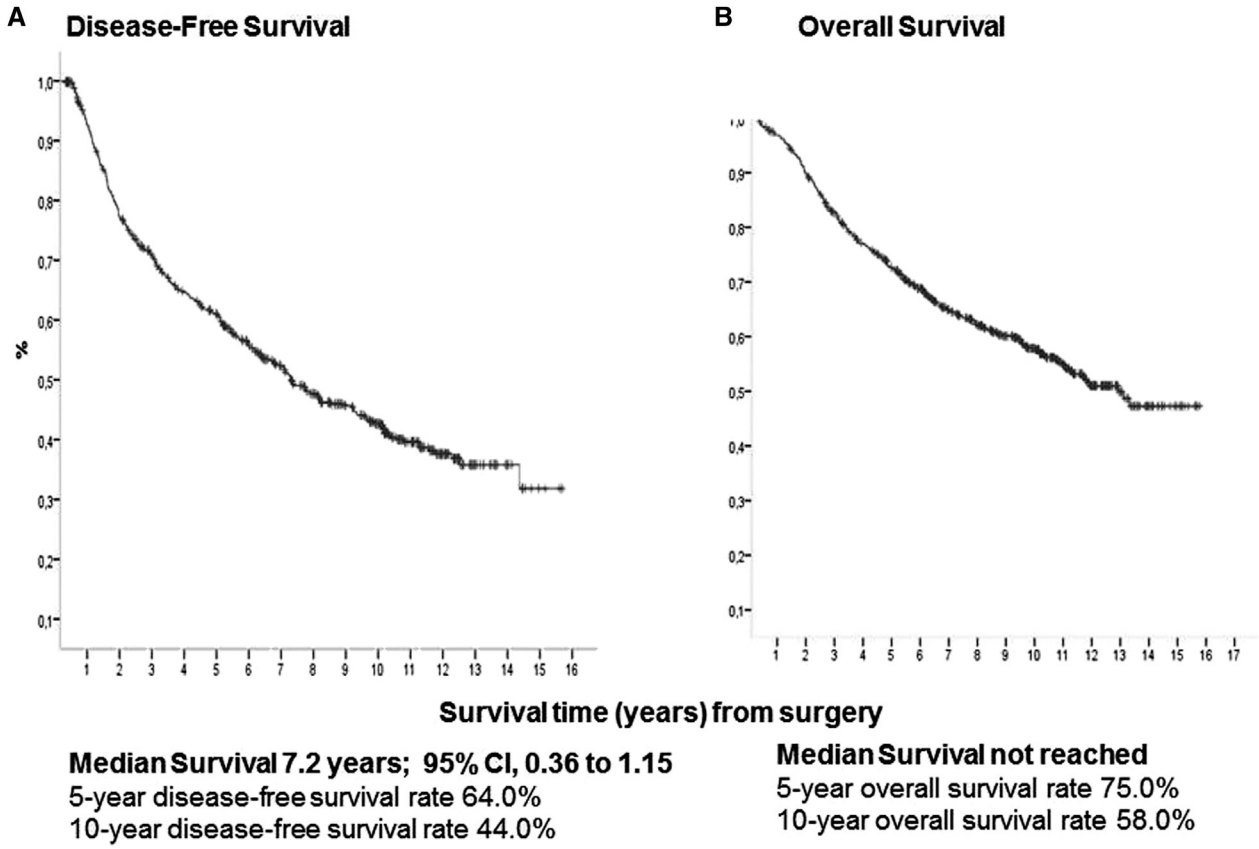


Figure 1. Kaplan-Meier curve of (A) DFS and (B) OS for the whole study population.

extremely poor prognosis and is usually present in very limited number in BC adjuvant studies. In keeping with both the important prognostic role of axillary node involvement, which is independent of biological parameters, together with the results of previous studies [10,19], the number of positive nodes indeed negatively affected OS in our series.

In our study age and menopause had no impact on outcome. However, many premenopausal women became

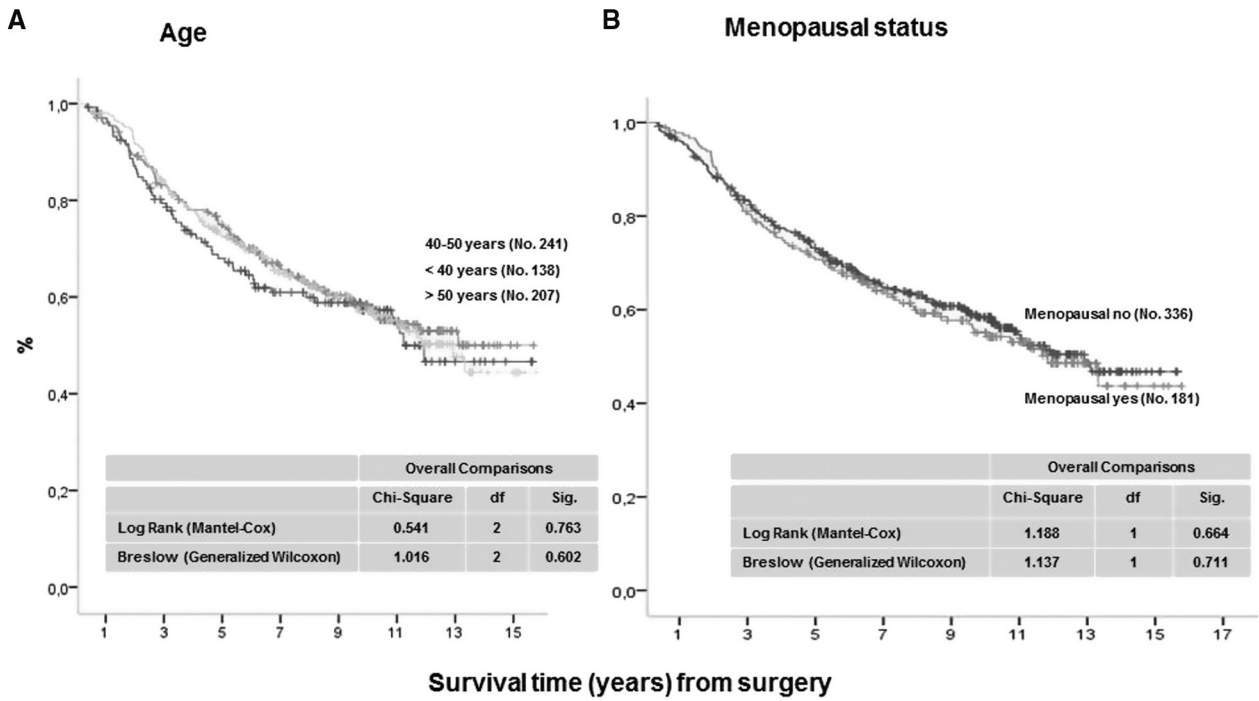
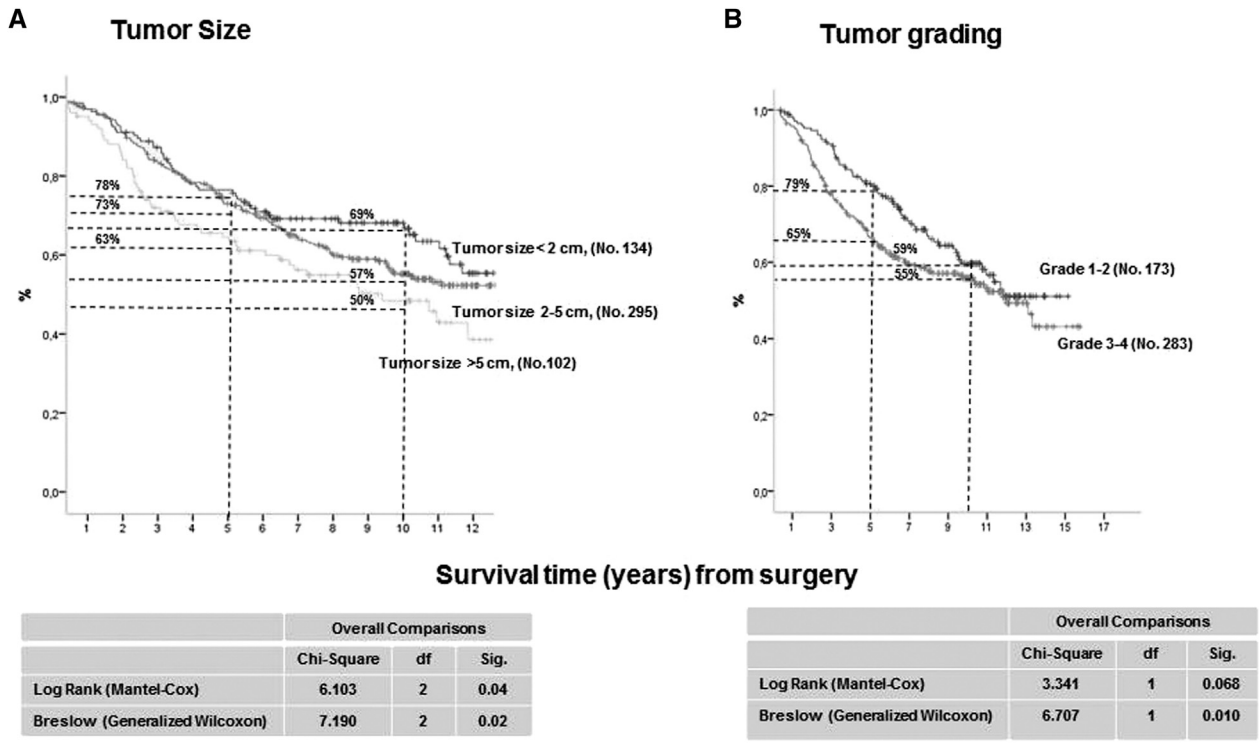


Figure 2. Kaplan-Meier estimates of OS in prespecified subset analyses by (A) age at surgery and (B) menopause status.



	Overall Comparisons		
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.103	2	0.04
Breslow (Generalized Wilcoxon)	7.190	2	0.02

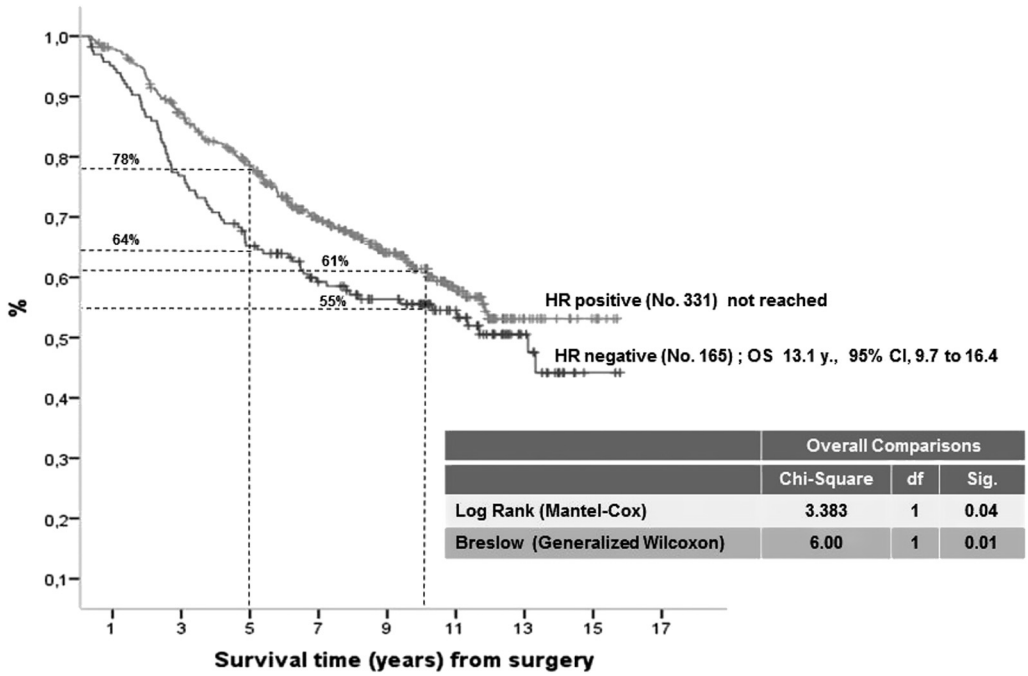
	Overall Comparisons		
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.341	1	0.068
Breslow (Generalized Wilcoxon)	6.707	1	0.010

Figure 3. Kaplan-Meier estimates of OS in prespecified subset analyses by (A) tumor size and (B) tumor grading.

persistently amenorrheic after HDC [9], and this may obscure any effects on outcome.

Patients with HR-positive BC had a significantly better survival. Positivity for HR is a known positive prognostic factor, characterized usually by more indolent disease. This allows 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 most HDC series [9,19,25]. More surprising is the more pronounced beneficial effect of HDC in small and low-grade tumors, which might be simply related to the better outcome of such populations. However, because it is known that a subgroup of luminal BC tumors that do not seem to be aggressive based on their immunohistochemical phenotype has a bad prognosis, HDC might have played a positive role in these tumors [26,27].

HER2-positive status did not affect DFS and OS in our series, in contrast with previous reports [10,28]. However,



	Overall Comparisons		
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.383	1	0.04
Breslow (Generalized Wilcoxon)	6.00	1	0.01

Figure 4. Kaplan-Meier estimates of median OS according to tumor HR status. 95% CI indicates 95% confidence interval.

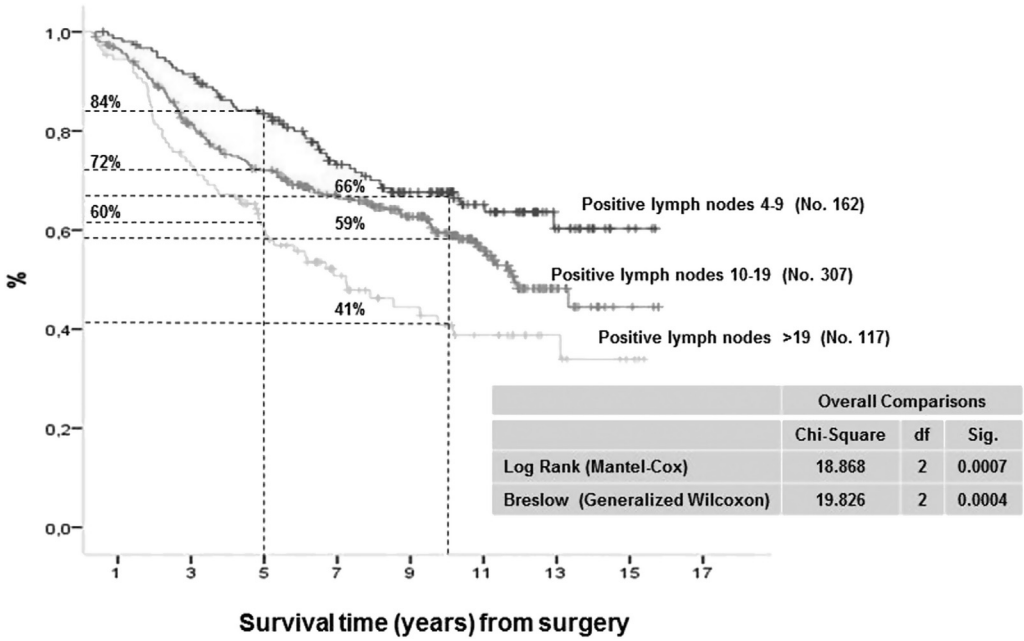


Figure 5. Kaplan-Meier estimates of median OS according to number of positive lymph nodes at surgery.

the survival curves diverge quite markedly in favor of the HER-negative group, suggesting that the lack of a statistically significant survival benefit might be in part related to the fact that only 32.4% of patients had HER2 status available. Therefore, the analysis was conducted in a limited proportion of our patients. A large Dutch study [10] showed greater DFS and OS in their HER2-negative population, and the authors suggested that the dose of anthracycline in patients harboring HER2-positive tumors should be increased. In our studies a significant number of HDC regimens included anthracyclines, mitoxantrone, and/or the introduction of anti-HER2 drugs in the adjuvant or metastatic phase. This may explain some differences from other series.

Unfortunately, TN disease was documented in only 35 patients, so the apparent beneficial results obtained in this high-risk population are largely insufficient to generate any hypothesis. However, Gluz et al. [28] found that the benefit of HDC was more evident in a basal-like phenotype (estrogen and progesterone receptor negative, HER2 negative, and basal cytokeratin positive) and in grade 3 tumors. Other authors have speculated that patients with TN tumors are the most likely to receive a benefit from HDC, because these cancers do not respond to endocrine therapy or other available targeted agents. The metastatic potential in TN BC is similar to that of other BC subtypes, but these tumors are associated with a shorter median time to relapse and death, as is also demonstrated in our small cohort.

Today, HDC with AHSCT has become a safe treatment modality with mortality rates [9,19,20] and quality-adjusted survival parameters [29] similar to conventional therapies. TRM and morbidity has progressively decreased from the mid-1990s, possibly related to the widespread switch from bone marrow hematopoietic progenitor cells to peripheral blood hematopoietic progenitor cells [30] and a better understanding of the whole procedure and supportive measures [31,32]. Moreover, HDC regimens associated with a high TRM are no longer used.

Most of the oncology community believes that HDC is no longer applicable now that we have entered the era of targeted therapies. Such a conclusion could be premature because the prognosis of high-risk BC has changed very little in the past 2 decades and particular novel targeted therapies have had an impact only in the subset of patients with BC overexpressing HER2. Moreover, in high-risk BC, 2 large European studies demonstrated an OS benefit of HDC consistent with the benefit in the HER2-negative and TN populations [9,10,28]. In the adjuvant setting of BC, a survival benefit, although limited, still means thousands of women being cured.

In conclusion, our study confirms that HDC and AHSCT in high-risk BC can now be given safely and with the needed dose intensification, with minimal early and late toxicity. Along with some more recent phase III studies, retrospective analyses, and, to some extent, the results from meta-analyses, our results suggest a potential role for HDC and AHSCT in high-risk BC. This approach may still represent a therapeutic option for carefully selected patients who harbor HER2-negative tumors and who have gross involvement of axillary lymph nodes. Further studies of HDC are advisable, taking into account the clinical and biological information we currently have, to select and target those patients more likely to benefit from chemotherapy given at higher than standard doses.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

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

Authorship statement: M.M., F.L., C.B., P.P., and M.Br. designed the study. M.M., F.L., G.R., C.B., M.Ba., P.P., and M.Br. performed quality control of data and algorithms. M.M., F.L., D.G., G.R., C.B., and P.P. conducted data analysis and interpretation. M.M., F.L., and P.P. performed statistical analysis. M.M., F.L., D.G., and P.P. prepared the manuscript. M.M., F.L., D.G., C.B., and P.P. edited the manuscript. All authors

reviewed the manuscript and approved the submitted and final versions.

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