

Randomized trial of high-dose adjuvant chemotherapy with autologous hematopoietic stem-cell support versus standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: overall survival after 6 years of follow-up

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Received 11 July 2007; revised 18 December 2007; accepted 11 January 2008

Investigation of high-dose chemotherapy (HD-CT) compared with standard-dose chemotherapy (SD-CT) as adjuvant treatment in patients with primary breast cancer and ≥ 10 axillary lymph nodes. From November 1993 to September 2000, 307 patients were randomized to receive after four cycles of epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²) i.v. (every 21 days) and either HD-CT of cyclophosphamide (1500 mg/m²), thiotepa (150 mg/m²) and mitoxantrone (10 mg/m²) i.v. for four consecutive days followed by stem cell transplantation or a SD-CT of three cycles CMF (cyclophosphamide 500 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m², i.v. on day 1 and 8, respectively, every 28 days). After a median follow-up of 6.1 years, 166 events with respect to event-free survival (EFS) (SD-CT: 91, HD-CT: 75) have been observed. The hazard ratio of HD-CT versus SD-CT is estimated as 0.80 [95% confidence interval (0.59, 1.08)], $P = 0.15$. The trend to a superiority of HD-CT as compared with SD-CT with respect to EFS seems to be more pronounced in premenopausal patients as compared with postmenopausal patients and in patients with tumor grade 3 as compared with patients with tumor grade 1/2. With a follow-up of 6 years, there was a trend in favor of HD-CT with respect to EFS not being significant. A proper meta-analysis needs to be undertaken for an evaluation of subgroups of patients who might benefit from HD-CT.

Key words: breast cancer, high risk, randomized study

introduction

Despite 20 years of clinical studies, the role of high-dose chemotherapy (HD-CT) in breast cancer is still controversial. Several nonrandomized studies have demonstrated improvement for patients with primary breast cancer which led to premature acceptance of this new treatment approach as a new standard of care for patients with high-risk breast cancer [1–5]. The initial enthusiasm was followed by a phase of

disillusionment after some of the randomized studies did not show a significant benefit and after a case of scientific misconduct [6–10]. HD-CT studies in breast cancer have been unpopular for the last 7 years. There is a new evidence that warrants an unbiased critical look at the 15 randomized studies including a total of ~6000 patients for patients with high-risk breast cancer [11–27]. We report the results of a 6-year follow-up analysis of the trial, which was first reported after a median follow-up of 3.8 years [22]. The study investigated the therapeutic effect of HD-CT cyclophosphamide, thiotepa and mitoxantrone, followed by autologous hemopoietic stem-cell support in a randomized trial compared with the standard-dose chemotherapy (SD-CT) as adjuvant treatment

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in patients with primary breast cancer and ≥ 10 positive axillary lymph nodes involved.

patients and methods

study design

In 1993, a prospective randomized multicenter trial was started in Germany for primary breast cancer patients with ≥ 10 positive axillary lymph nodes without distant metastases to investigate the effect of a HD-CT followed by autologous hematopoietic stem-cell support as compared with a SD-CT.

The principal eligibility criteria were a histologically proven primary breast cancer of stage pT1–3 or pT4b, pN > 9 and M0. For further inclusion and exclusion criteria, see Zander et al. [22].

The primary local treatment was a mastectomy or breast conserving surgery with axillary dissection with at least 10 identifiable and involved lymph nodes in the specimen. After four cycles of EC (epirubicin 90 mg/m², cyclophosphamide 600 mg/m², i.v. every 21 days), patients received HD-CT of CTM (HD-CTM: cyclophosphamide 1500 mg/m², thiotepa 150 mg/m², mitoxantrone 10 mg/m², i.v. on four consecutive days) followed by autologous hematopoietic stem-cell support or a SD-CT of three cycles CMF [cyclophosphamide 500 mg/m², methotrexate 40 mg/m², 5-fluorouracil (5-FU) 600 mg/m², i.v. on days 1 and 8 every 28 days]. Chemotherapy with EC should start within 42 days postoperation. A protocol amendment defined that patients with estrogen receptor (ER) or progesterone receptor (PR)-positive tumors should be treated with tamoxifen.

follow-up

Patients were followed up at regular intervals to ensure detection of any kind of recurrence at the earliest time possible. Examinations were scheduled to be carried out every 6 months. This was carried out until April 2002. At that time after a median follow-up of ~ 3.8 years, a first analysis of the study was carried out [22]. Mid-2004 the participating centers were contacted for a documentation of the actual follow-up status of the patients. This was completed in January 2005. The completeness of follow-up was calculated as proposed by Clark et al. [28].

statistical methods

All data storage and analysis were carried out using the Statistical Analysis System [29]. All data analysis were carried out according to a prespecified analysis plan already used for the first analysis of the study [22]. The analysis was carried out on an intention-to-treat basis. All analyses including prognostic factors were on the basis of patients for whom all prognostic factors were completely documented. The event-free survival (EFS) rates and the overall survival (OS) rates were calculated according to the Kaplan–Meier method and comparison was made by the log-rank test [30, 31]. The hazard ratio between different groups defined by treatment or prognostic factors with corresponding confidence intervals (CIs) were determined by the Cox regression model [32]. Tests were carried out with the Wald test. For a simultaneous assessment of the effects of treatment and prognostic factors and for the investigation of interactions between treatment and the factors, menopausal status, tumor grade and ER status, the same methods as in Zander et al. [22], were used.

results

study population

From November 1993 to September 2000, 307 patients were randomly assigned from 36 centers. A total of 152 patients were randomly assigned to the high-dose arm (HD-CT), and 155

patients were randomly assigned to the standard arm (SD-CT). Three centers with a total of five randomized patients had to be excluded due to the lack of cooperation of the patients after randomization. Thus, all analyses are restricted to 302 randomly assigned patients who had been entered from 33 institutions (SD-CT 152 patients, HD-CT 150 patients).

As described previously [22], entry criteria of the trial were violated for 13 patients in treatment arm SD-CT and for 5 patients in treatment arm HD-CT. None of these patients were excluded from the analyses. For a description of the study population with respect to baseline patient and tumor characteristics and of the compliance of the patients to the randomized treatment regimens, see reference [22].

follow-up and observed events

Patients were followed until January 2005 leading to a median follow-up time of 6.1 years (SD-CT 6.1 years, HD-CT 6.2 years). The status and completeness of follow-up is displayed in Table 1.

Table 2 shows the distribution of the patients to the different types of event of failure. A total of 166 events occurred with respect to the end point EFS (SD-CT 91 versus HD-CT 75). Twenty-two patients experienced an isolated locoregional recurrence as first event of failure (SD-CT 11 versus HD-CT 11), 140 patients had distant failure with or without simultaneous local failure as first event (78 versus 62) and 4 patients died without previous event (2 versus 2). A total of 123 events occurred with respect to the end point OS (SD-CT 66 versus HD-CT 57).

comparison of the treatment arms with regard to EFS

The hazard ratio of HD-CT versus SD-CT is estimated as 0.80 [95% CI (0.59, 1.08)]. This effect is not significant

Table 1. Status of follow-up

	SD-CT, n = 152	HD-CT, n = 150
Follow-up regarding EFS		
Complete until event	91	75
Event not yet observed	61	75
>5 years follow-up	37	53
3–5 years follow-up	15	13
1–3 years follow-up	3	2
<1 year follow-up	6	7
Follow-up regarding OS		
Complete until death	66	57
Death not yet observed	86	93
>5 years follow-up	56	65
3–5 years follow-up	18	17
1–3 years follow-up	5	4
<1 year follow-up	7	7
Completeness of follow-up	86%	88%
Median follow-up (in years)	6.1	6.2

SD-CT, standard-dose chemotherapy; HD-CT, high-dose chemotherapy; EFS, event-free survival; OS, overall survival.

($P = 0.15$). The corresponding EFS rates are displayed in Figure 1. There seems to be a slight superiority of HD-CT as compared with SD-CT emerging 2 years after primary surgery. Estimated EFS rate after 5 years is 42% [95% CI (34%, 50%)] in treatment arm SD-CT and 49% (95% CI [40%, 57%]) in treatment arm HD-CT. As mentioned before, this difference is not significant.

The results of the multivariate analysis of treatment and the prognostic factors, number of positive lymph nodes, degree of lymph node involvement, tumor grade, ER and PR status, on EFS are not shown in detail. They are similar to the results shown before [22]. In this analysis, where the treatment effect is adjusted for the prognostic factors, the hazard ratio of HD-CT versus SD-CT is estimated as 0.78 [95% CI (0.56, 1.09)]. This effect is not significant ($P = 0.15$).

The results of the analyses regarding interactions between treatment and the prognostic factors, menopausal status, tumor grade and ER status, with respect to EFS are also not shown in detail. They are similar to the results shown

Table 2. Distribution of events of failure

	SD-CT, <i>n</i> = 152	HD-CT, <i>n</i> = 150	Total, <i>n</i> = 302
First event of failure			
Isolated locoregional recurrence	11	11	22
Distant failure	78	62	140
Distant metastases	70	55	125
Second cancer breast	5	5	10
Second cancer distant	3	2	5
Death without recurrence	2	2	4
Status			
Alive without recurrence	61	75	136
Alive with recurrence	25	18	43
Death without recurrence	2	2	4
Death after recurrence	64	55	119
Number of events for EFS	91	75	166
Number of events for OS	66	57	123

SD-CT, standard-dose chemotherapy; HD-CT, high-dose chemotherapy; EFS, event-free survival; OS, overall survival.

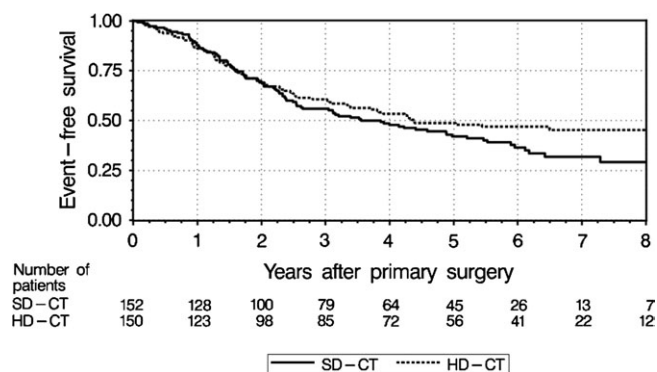


Figure 1. Event-free survival rate by treatment arm.

before [22]. No significant interaction can be demonstrated. The trend to a superiority of HD-CT as compared with SD-CT with respect to EFS seems to be more pronounced in premenopausal patients as compared with postmenopausal patients and in patients with tumor grade 3 as compared with patients with tumor grade 1/2. But these differences are not significant.

comparison of the treatment arms with regard to OS

With respect to the end point OS, 123 events have been observed. Sixty-six events occurred in treatment arm SD-CT, and 57 events occurred in treatment arm HD-CT. The hazard ratio of HD-CT versus SD-CT is estimated as 0.84 [95% CI (0.59, 1.20)]. This effect is not significant ($P = 0.33$). The corresponding OS rates are displayed in Figure 2. The estimated 5-year OS rate was 62% [95% CI (54%, 70%)] in the standard arm and 64% [95% CI (56%, 72%)] in the high-dose arm.

Table 3 shows the results of the multivariate analysis of treatment and prognostic factors on OS. In this analysis, the treatment effect is adjusted for the prognostic factors, number of positive lymph nodes, degree of lymph node involvement, tumor grade, ER and PR status. The hazard ratio of HD-CT versus SD-CT in the adjusted analysis is estimated as 0.76 [95% CI (0.51, 1.12)]. This effect is not significant ($P = 0.16$). The factors, tumor size and ER status, show an effect on OS on the 5% level.

Table 4 shows the results of the analyses regarding interactions between treatment and the prognostic factors, menopausal status, tumor grade and ER status, with respect to OS, i.e. it was analyzed whether the effect of HD-CT versus SD-CT on OS is heterogeneous in prognostic subgroups of patients defined by these factors. The tests for interactions are carried out with significance level 1%. As shown in Table 4, no significant interaction can be demonstrated. For a quantification of treatment effects in the subgroups defined by each of the factors, menopausal status, tumor grade and ER status, the hazard ratios between the treatment groups with 99% CIs are displayed in Table 4. Additionally, the OS rates in the different subgroups are shown in Figure 3.

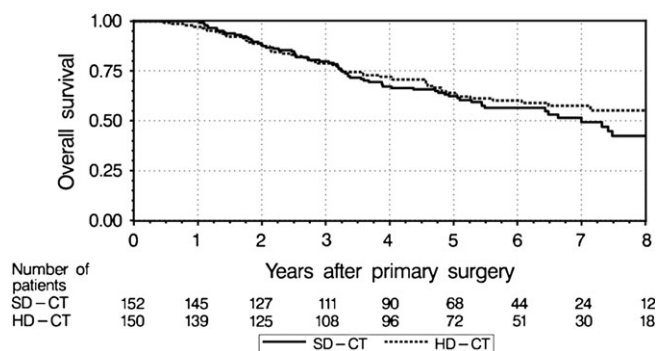


Figure 2. Overall survival rate by treatment arm.

Table 3. Multivariate analysis of effect of treatment and effects of prognostic factors on OS

	Hazard ratio	95% CI	P value
Treatment			
SD-CT	1.00	–	0.16
HD-CT	0.76	(0.51, 1.12)	
Number of positive lymph nodes			
10–15	1.00	–	0.21
≥16	1.28	(0.87, 1.87)	
Degree of lymph node involvement			
<100% positive	1.00	–	0.10
=100% positive	0.54	(0.26, 1.13)	
Tumor size (in mm)			
≤30	1.00	–	0.004
>30	1.76	(1.20, 2.58)	
Tumor grade			
1/2	1.00	–	0.15
3	1.34	(0.90, 2.00)	
Estrogen receptor status			
Positive	1.00	–	0.008
Negative	1.91	(1.19, 3.07)	
Progesterone receptor status			
Positive	1.00	–	0.97
Negative	0.99	(0.62, 1.60)	

Patients with complete data for all prognostic factors: *n* = 267, 130 SD-CT, 137 HD-CT, 112 events.

OS, overall survival; SD-CT, standard-dose chemotherapy; HD-CT, high-dose chemotherapy; CI, confidence interval.

Table 4. Interactions between treatment and the prognostic factors, menopausal status, tumor grade and ER status, with regard to OS

Prognostic factor	Patient population	Hazard ratio ^a HD-CT versus SD-CT with 99% CI	Interactive effect with 99% CI	P value for test of interaction
Menopausal status	Pre	0.79 (0.41, 1.55)	1.00 (0.37, 2.67)	0.99
	Post	0.79 (0.38, 1.65)		
Tumor grade	1/2	0.95 (0.41, 2.18)	0.75 (0.27, 2.12)	0.48
	3	0.71 (0.38, 1.33)		
ER status	Positive	0.60 (0.29, 1.24)	1.71 (0.63, 4.68)	0.17
	Negative	1.02 (0.51, 2.04)		

Patients with complete data for all prognostic factors: *n* = 267, 130 SD-CT, 137 HD-CT, 112 events.

^aSeparate Cox models including the factors menopausal status, tumor grade, ER status, number of positive lymph nodes, tumor size and factor-specific treatment effects.

ER, estrogen receptor; OS, overall survival; HD-CT, high-dose chemotherapy; SD-CT, standard-dose chemotherapy; CI, confidence interval.

discussion

In this paper, we present the results of a 6.1-year follow-up of our randomized study comparing high-dose mitoxantrone, cyclophosphamide and thiotepa with SD-CT. The first

publication of this study with the follow-up of 3.8 years revealed a trend toward better EFS for the high-dose arm [hazard ratio 0.75, 95% CI (0.54, 1.06), *P* = 0.095]. The present analysis with longer follow-up and 166 events observed still shows a trend in favor of HD-CT with a hazard ratio of 0.80, 95% CI (0.59, 1.08), *P* = 0.15. But, despite the added follow-up including now 6.1 years, there is no significant difference between the two treatment arms. The trend to a superiority of HD-CT as compared with SD-CT with respect to EFS seems to be more pronounced in premenopausal patients as compared with postmenopausal patients and in patients with tumor grade 3 as compared with patients with tumor grade 1/2. But these differences are not significant. Thus, the results of our first analysis are confirmed.

The present paper describes for the first time detailed results with respect to OS. With 123 deaths observed, no difference between the treatment arms can be detected [hazard ratio of HD-CT versus SD-CT 0.84, 95% CI (0.59, 1.20), *P* = 0.33]. No interactions between treatment and the prognostic factors, menopausal status, tumor grade and ER status, with respect to OS could be detected. It has to be mentioned that the number of events for OS, i.e. 123, is still rather low so that the CIs are relatively large and the power to detect differences is accordingly small. The subgroup with the largest estimated effect of HD-CT were patients with ER-positive tumors. As suggested by a referee, we carried out an additional subgroup analysis in the group of 100 premenopausal patients with ER-positive tumors. The estimated hazard ratio of HD-CT versus SD-CT was 0.48, 99% CI (0.17, 1.34), *P* = 0.065, but all subgroup analyses should be interpreted cautiously.

Histopathologic analysis of specimen from 188 of 302 patients showed that Her2/neu and Bcl-2 were prognostic for EFS, but not predictive for response to standard- or high-dose therapy, whereas p53-positive patients benefited from high-dose therapy [33]. Further histopathologic and genetic studies might give further insight to response prediction to high-dose chemotherapy.

Fifteen randomized studies with a total of ~6000 patients were carried out in patients with high-risk breast cancer. Several of those have been reported with a median follow-up of >5 years.

Some of these studies also included patients with four or more [14, 15, 18, 19, 24, 27] or with eight or more [16, 17] positive lymph nodes. Eight studies [8, 12, 13, 20, 21, 23, 25, 26] included the same study population as our study, i.e. only patients with ≥10 positive lymph nodes. To put our results into context, Table 5 shows the OS rates of both treatment arms (SD-CT and HD-CT) of all eight studies including only patients with ≥10 positive lymph nodes. International Breast Cancer Study Group (IBCSG) [23] also included 91 patients with five to nine positive lymph nodes if they had ER-negative or stage III tumors, and the study by Hortobagyi [8, 26] also included 30 patients with four to nine positive lymph nodes after neo-adjuvant chemotherapy. These patients were not reported separately and thus included in Table 5. Taking into account the variability of these results due to rather large CIs in studies with a low number of deaths, the OS rates can be regarded as of similar

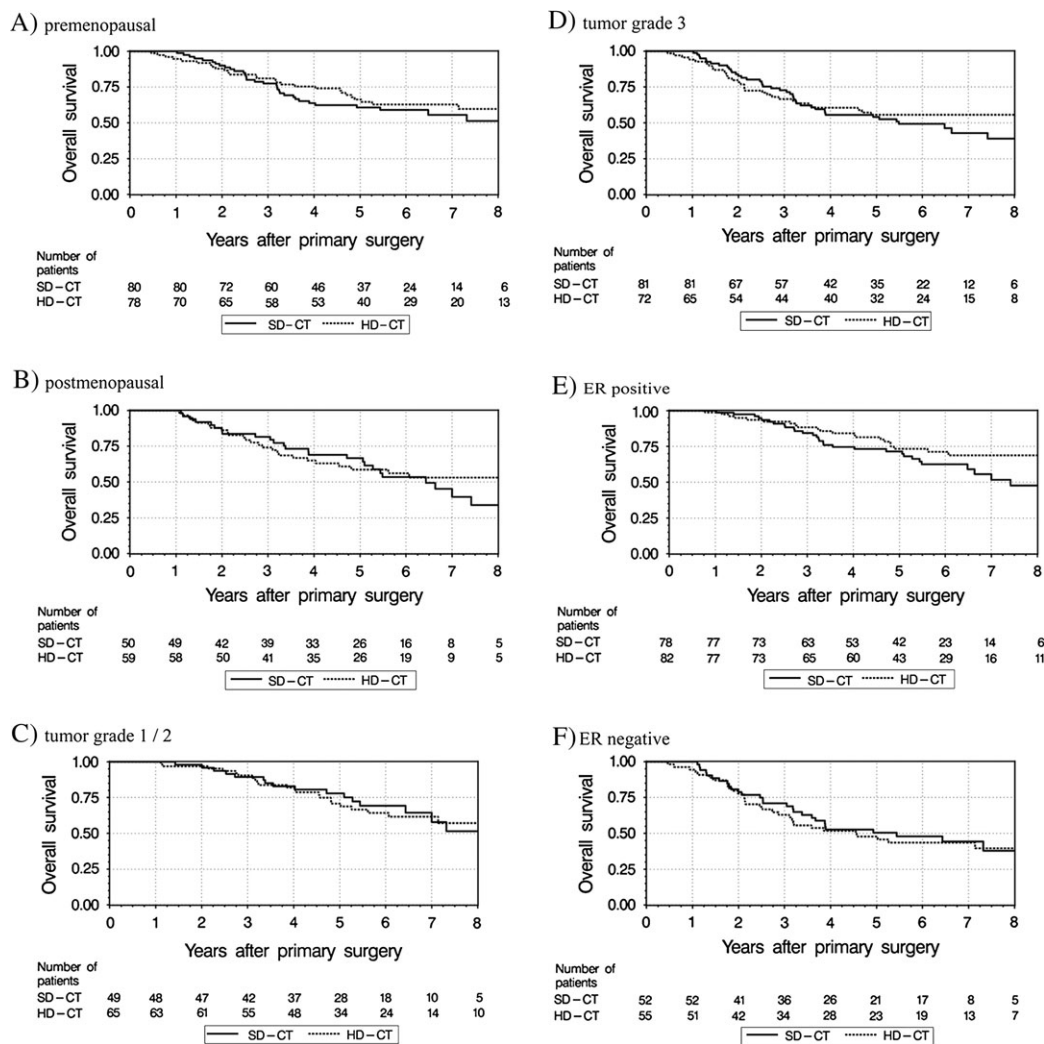


Figure 3. Overall survival rate by treatment arm in prognostic subgroups defined by menopausal status, tumor grading, and ER status. (A) Premenopausal, (B) postmenopausal, (C) tumor grade 1/2, (D) tumor grade 3, (E) ER positive and (F) ER negative.

magnitude. All studies show much higher OS rates than previous studies in the same patient population not investigating HD-CT [34], illustrating again that the group of patients for whom HD-CT is intended is a strong positive selection.

What do the total of >6000 patients with high-risk primary breast cancer randomized to HD-CT or conventional chemotherapy teach us about the value of HD-CT?

Three studies with <100 involved patients are too small to give information beyond the feasibility of the procedure [8, 13, 21, 26]. The study by Bergh et al. [17] is impaired by the design that the conventional group got more intensive chemotherapy than the high-dose arm.

The studies by Gianni and Bonadonna [14], Peters et al. [12], Leonard et al. [15], Tallman et al. [20], Coombes et al. [24] and Bearman et al. [27] showed no improvement on OS and EFS. The studies by Rodenhuis et al. [18, 19] and by the IBCSG [23] showed a trend in favor of HD-CT with respect to EFS and with respect to OS but this was not significant.

The study by Nitz et al. [25] showed a significant difference in EFS and OS. The study is remarkable for its design and its

results. It compares tandem-HD-CT, cyclophosphamide, thiotepa and epirubicin after two courses of dose-dense epirubicin and cyclophosphamide regimen with a dose-dense conventional chemotherapy consisting of four courses of EC, followed by three courses of CMF. The chemotherapy regimen used in the SD-CT arm of Nitz et al. seems to be similar to that used in our study, but there are differences. In the study by Nitz et al., the four courses of EC and three courses of CMF are applied over a period of 12 weeks, whereas in our study they are applied over a period of 21 weeks. That is the reason why their SD-CT regimen is called dose dense. On the other hand, it has to be noted that the total dose applied in the three CMF courses in the study by Nitz et al. (cyclophosphamide 1800 mg/m², methotrexate 120 mg/m², 5-FU 1800 mg/m²) is much lower than in our study (cyclophosphamide 3000 mg/m², methotrexate 240 mg/m², 5-FU 3600 mg/m²). An interesting observation is that the 5-year OS rates of the SD-CT arm of Nitz et al. and of our SD-CT arm are very similar (see Table 5).

The French PEGASE-01-study by Roche et al. [16] which included 314 patients with more than seven involved lymph nodes reported as results of an interim analysis conducted in

Table 5. Overview of 5-year OS rates in all eight studies investigating patients with ≥ 10 positive lymph nodes

Study	Treatments (SD-CT and HD-CT)	Regimens	Patients	Median follow-up (years)	Deaths	5-year OS rate	
						SD-CT (%)	HD-CT (%)
Hortobagyi et al. [8]; Hanrahan et al. [26]	8× FAC; 8× FAC + 2× HD-CEP	FAC: 1000 mg/m ² 5-FU, 150 mg/m ² doxorubicin, 500 mg/m ² cyclophosphamide; HD-CEP: 5.25 g/m ² cyclophosphamide, 1200 mg/m ² etoposide, 165 mg/m ² cisplatin	78	11.9	47	66.7	50.7
Schrama et al. [13]	4× FE ₁₂₀ C; 4× FE ₁₂₀ C + HD-CTC	FE ₁₂₀ C: 500 mg/m ² 5-FU, 120 mg/m ² epirubicin, 500 mg/m ² cyclophosphamide; HD-CTC: 6 g/m ² cyclophosphamide, 480 mg/m ² thiotepa, 1600 mg/m ² carboplatin	81	6.9	41	62.5	61
Tokuda et al. [21] ^a	6× FAC; 6× FAC + HD-CT	FAC: 500 mg/m ² 5-FU, 40 mg/m ² doxorubicin, 500 mg/m ² cyclophosphamide; HD-CT: 6 g/m ² cyclophosphamide, 600 mg/m ² thiotepa	97	?	?	66	67
Zander et al. (this analysis)	4× EC + 3× CMF; 4× EC + HD-CTM	EC: 90 mg/m ² epirubicin, 600 mg/m ² cyclophosphamide; CMF: 1000 mg/m ² cyclophosphamide, 80 mg/m ² methotrexate, 1200 mg/m ² 5-FU; HD-CTM: 6 g/m ² cyclophosphamide, 600 mg/m ² thiotepa, 40 mg/m ² mitoxantrone	302	6.1	123	62	64
IBCSG [23]	4× AC/EC + 3× CMF; 3× ID-EC	AC/EC: 150 mg/m ² doxorubicin, 90 mg/m ² epirubicin, 600 mg/m ² cyclophosphamide; CMF: 1400 mg/m ² cyclophosphamide, 80 mg/m ² methotrexate, 1200 mg/m ² 5-FU; ID-EC: 200 mg/m ² epirubicin, 4 g/m ² cyclophosphamide	344	5.8	133	61	70
Nitz et al. [25] ^b	4× EC + 3× CMF; × EC + 2× HD-ETC	EC: 90 mg/m ² epirubicin, 600 mg/m ² cyclophosphamide; CMF: 600 mg/m ² cyclophosphamide, 40 mg/m ² methotrexate, 600 mg/m ² 5-FU; HD-ETC: 90 mg/m ² epirubicin, 3 g/m ² cyclophosphamide, 400 mg/m ² thiotepa	403	4	127	60	75
Tallman et al. [20] ^b	6× FAC; 6× FAC + HD-CT	FAC: 1000 mg/m ² 5-FU, 60 mg/m ² doxorubicin, 1400 mg/m ² cyclophosphamide; HD-CT: 6 g/m ² cyclophosphamide, 800 mg/m ² thiotepa	511	6.1	?	67	65
Peters et al. [12]	4× FAC + ID-CPB; 4× FAC + HD-CPB	FAC: 1200 mg/m ² 5-FU, 60 mg/m ² doxorubicin, 600 mg/m ² cyclophosphamide; ID-CPB: 2.7 g/m ² cyclophosphamide, 90 mg/m ² cisplatin, 90 mg/m ² carmustine; HD-CPB: 5.625 g/m ² cyclophosphamide, 165 mg/m ² cisplatin, 600 mg/m ² carmustine	785	7.3	294	71	71

?, data not given.

^aOS rate not at 5 years, but at 4 years.

^bFive-year OS rate was not explicitly stated in the publication. It was read off the figures showing Kaplan–Meier estimates of OS rate. OS, overall survival; SD-CT, standard-dose chemotherapy; HD-CT, high-dose chemotherapy; 5-FU, 5-fluorouracil.

2001 3-year disease-free-survival rates of 71% in the high-dose group versus 55% in the standard-dose group, $P = 0.002$. At that time, no significant difference could be shown in OS. A further analysis presented at a breast cancer meeting in Ravenna in 2004 yielded a significant difference in OS in favor of the high-dose therapy.

The Italian study by Gianni and Bonadonna [14] showed only a marginal difference in 5-year progression-free survival rates in the whole study group of 382 patients, but a trend of a better progression-free survival for the 112 patients under 36 years of age (hazard ratio 0.66) and for the 147 patients with four to nine positive lymph nodes (hazard ratio 0.69).

The Dutch study by Rodenhuis et al. [18, 19] yielded for the entire group of 885 patients marginal improvement in relapse-free survival by HD-CT with a 5-year relapse-free survival rate of 59% in the SD-CT arm versus 64% in the HD-CT arm. Subgroup analyses showed that HD-CT seems to be more effective in patients with ≥ 10 positive axillary nodes, in younger patients, in patients with low tumor grade and in patients with Her2/neu-negative tumors.

The study by the IBCSG [23] showed for the whole study group of 344 patients a trend in favor of HD-CT with respect to EFS and OS. In an analysis of which subgroups of patients might benefit most from HD-CT, no interactions between treatment and various prognostic factors could be detected. The trend to a superiority of HD-CT as compared with SD-CT seemed to be more pronounced in patients with ER-positive breast cancer (for EFS: hazard ratio 0.58, $P = 0.02$; for OS: hazard ratio 0.53, $P = 0.05$) and those with primary tumors 2–5 cm (for EFS: hazard ratio 0.51, $P < 0.01$; for OS: hazard ratio 0.65, $P = 0.08$).

Sequential dose-intense chemotherapy has been discussed as an alternative strategy to overcome resistance [35, 36]. A comparison of HD-CT and dose-intense chemotherapy in patients with operable breast cancer involving 4+ axillary nodes shows comparable results [37].

Unfortunately, most studies in the field of high-dose therapy were underpowered [38]. Since most studies being beyond 5 years of follow-up, a proper meta-analysis needs to be undertaken for an evaluation of subgroups of patients who might benefit from this treatment approach. The systematic review conducted by the Cochrane Collaboration [39] is insufficient to answer this question. As a first point, the statistical methods used in this review for the meta-analysis of time-to-event data are questionable. Different analyses were carried out at different time points of follow-up including a variable number of studies dependent at which time point EFS rates or OS rates were reported in the cited studies. This procedure does not allow conclusions at which time point in follow-up differences between the treatment groups exist or not. Instead, proper analysis techniques for the meta-analysis of time-to-event data should have been used [40, 41]. As a second point, the analysis of interactions between treatment and prognostic factors, which is required for the detection of subgroups of patients who might benefit from HD-CT, is only possible in an individual patient data meta-analysis. This is currently being conducted under direction of the MD Anderson

Cancer Center, and the individual data of our study will be included in this analysis.

funding

Dr Mildred Scheel Stiftung der Deutschen Krebshilfe, Hamburger Krebsgesellschaft; Erich and Gertrud Roggenbuck Foundation; BMBF to C.S.

acknowledgements

Participating centers: Universitätsklinikum Hamburg-Eppendorf, Hamburg; Universitätsklinikum, Ulm; Klinikum Oldenburg gGmbH; Klinikum Benjamin Franklin, Berlin; Humaine Klinikum, Bad Saarow; Klinikum der Charité, Berlin; Klinikum 5. Medizinische Klinik, Nürnberg; Universitätskliniken des Saarlandes, Homburg; Universitätsklinikum, Kiel; Evangelische Diakonissenanstalt, Bremen; Klinikum der Otto-von-Guericke-Universität, Magdeburg; Universitätsklinikum, Mainz; Universitätsklinikum, Münster; Medizinische Universität, Lübeck; Zentralkrankenhaus, Bremen; Klinikum der Universität, Rostock; Städtische Kliniken, Kassel; Krankenhaus; Kaiserslautern; Stiftung Deutsche Klinik für Diagnostik GmbH, Wiesbaden; Krankenhaus Neukoelln, Berlin; Franziskus Hospital, Bielefeld; Klinikum rechts der Isar, München; Städtische Krankenhaus, Idar-Oberstein; St Josefs-Hospital, Cloppenburg; Onkologische Praxis Prof Dr Kleeberg, Hamburg; Universitätsklinikum, Dresden; Klinikum Chemnitz gGmbH, Chemnitz; Klinikum der Philipps-Universität, Marburg; Dr Horst-Schmidt-Klinikum, Wiesbaden; Kantonspital, Basel; Klinikum Ernst von Bergmann, Potsdam; Campus Virchow-Klinikum, Berlin; Klinikum der Universität, Göttingen; Städtisches Krankenhaus Süd, Lübeck; Klinikum der J.W. von Goethe Universität, Frankfurt/Main.

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