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European Journal of Cancer 37 (2001) 1123–1131

European Journal of Cancer

www.ejconline.com

Long-term prognosis of breast cancer patients with 10 or more positive lymph nodes treated with CMF

C. Schmoor [a,*], W. Sauerbrei [a], G. Bastert [b], H. Bojar [c], M. Schumacher [a]
for the German Breast Cancer Study Group (GBSG)

[a] *Institute of Medical Biometry and Medical Informatics, University of Freiburg, Stefan-Meier-Str. 26, D-79104 Freiburg, Germany*
[b] *Department of Gynaecology, University of Heidelberg, Germany*
[c] *Department of Chemical Oncology, University of Düsseldorf, Germany*

Received 24 August 2000; received in revised form 14 February 2001; accepted 23 February 2001

Abstract

The purpose of this investigation was to study the long-term prognosis of breast cancer patients with 10 or more positive lymph nodes after conventional chemotherapy treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Between 1984 and 1989, 1048 node-positive patients were treated with CMF in two separate trials conducted by the German Breast Cancer Study Group (GBSG). Subgroups either received radiotherapy or tamoxifen in addition. In this study, long-term prognosis in the subgroup of 141 patients with 10 or more positive lymph nodes was investigated. Univariate and multivariate Cox models were used to evaluate the effect of prognostic factors on event-free survival (EFS) and overall survival (OS). Both univariate and multivariate analyses revealed the progesterone receptor (PR) status as the dominating prognostic factor for both EFS and OS, resulting in a strongly increased risk of more than 2-fold for receptor-negative patients. A large number of positive lymph nodes also affected the prognosis for EFS. In univariate analysis, the degree of lymph node involvement (i.e. percentage of positive nodes out of all examined nodes), oestrogen status (ER) status, and tumour grade also showed significant effects. To conclude, the prognosis in the subgroup of patients with 10 or more positive lymph nodes is heterogeneous. Some surprisingly high survival rates have been observed in case series of breast cancer patients treated with high-dose chemotherapy which may be explained by patient selection. From the usual factors investigated in this study, the PR status showed the strongest effect, and, at least this factor should be taken into account in the design and analysis of trials for breast cancer patients with a poor prognosis.

Keywords: Breast neoplasms; Prognosis; Clinical trial

1. Introduction

Although adjuvant polychemotherapy treatment for breast cancer patients has led to improvements in both event-free survival (EFS) and overall survival (OS) [1], patients with 10 or more positive lymph nodes still have a high rate of recurrence, and EFS rates after five years are below 50% [2–4]. Therefore, the improvement of this poor prognosis by applying new treatment strategies, such as high-dose chemotherapy, is considered as one of the most important topics of current research in breast cancer. Several observational studies have reported EFS and OS rates after treatment with high-dose chemotherapy as being substantially larger than the corresponding rates from a retrospectively chosen control group. However, detailed information about other potential prognostic factors or possible selection criteria for the patients treated with high-dose chemotherapy is often not given [5]. This may be due to the assumption that a further separation of patients with 10 or more positive lymph nodes in subgroups of patients with different prognosis is not possible on account of the strong prognostic effect of the number of positive lymph nodes.

This may explain the limited interest in this issue in the literature. Recently, Schmoor and Schumacher [4]

* Corresponding author. Tel.: +49-761-270-7371; fax: +49-761-270-7373.
E-mail address: cs@imbi.uni-freiburg.de (C. Schmoor).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00090-9

reported a 5-year OS rate in a group of patients with 10 or more positive nodes treated with conventional chemotherapy of approximately 40%. For this poor prognosis group, we therefore wanted to investigate the prognostic value of standard factors for 141 patients with 10 or more positive nodes with a median follow-up of approximately 10 years. These patients represent a subgroup (13%) of 1048 lymph node-positive patients who were all treated with adjuvant conventional chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil; CMF) within two studies of the German Breast Cancer Study Group (GBSG).

2. Patients and methods

2.1. Study design

In 1984, the GBSG started two studies (GBSG studies 2 and 3) in patients with primary histologically proven node-positive breast cancer without known distant metastatic spread to compare different adjuvant treatment regimens. Primary local treatment was a modified radical mastectomy (Patey) with *en bloc* axillary dissection with at least six identifiable lymph nodes in the specimen. Patients were younger than 65 years old and had a Karnofsky index of at least 60. During the recruitment period, the studies were opened also to older patients, if they were in a very good clinical condition. The studies were performed after approval by an ethical committee. Informed consent was obtained from each patient.

Between 1984 and 1989, 1048 patients from 63 clinical institutions entered these studies, which have been previously described [6–9]. The studies were originally intended as randomised trials, but actually planned as comprehensive cohort studies [6,10] including also eligible patients who refused randomisation because of a preference to be in one of the treatment arms under study. 672 (64%) of the patients were randomised. GBSG study 2 had a two by two factorial design. Patients were allocated to receive either three or six cycles chemotherapy, on the one hand, and to receive either 2 years of hormonal treatment with tamoxifen or no hormonal therapy on the other hand. According to statements of the National Cancer Institute (NCI) consensus conference [11] in December 1986, the protocol was modified with premenopausal patients being randomised only with respect to the duration of chemotherapy without receiving tamoxifen. GBSG study 3 was designed to investigate the effect of adjuvant radiotherapy in addition to the six cycles of chemotherapy.

In 141 (13%) of the 1048 patients included, 10 or more positive axillary lymph nodes were found at the time of primary diagnosis. All analyses presented in this paper are based on these 141 patients.

2.2. Adjuvant treatment

Chemotherapy was administered according to the modified Bonnadonna CMF regimen consisting of 500 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 600 mg/m^2 5-fluorouracil given intravenously (i.v.) on days 1 and 8 of a 4-week treatment period. The first CMF cycle was to be started within 36 h after mastectomy. Hormonal therapy in GBSG study 2 consisted of a daily dose of 30 mg tamoxifen over a period of 2 years. Radiotherapy in GBSG study 3 was administered between the second and third cycle of CMF. The target volume included the chest wall, the parasternal and supraclavicular nodes, and the axilla. The recommended beam energy was 4–6 MV-photons or telecobalt. Conventional fractionation (five times weekly, 2 Gy) was used. The chest wall was irradiated by tangential fields (reference point in the chest wall in 2 cm depth) up to 50 Gy. The parasternal and supraclavicular nodes and the axilla were included in an anterior field ('hockey stick', reference point in 3 cm depth). The total dose was 44 Gy. In the parasternal region, half of the dose was to be administered with electrons, if available.

2.3. Determination of prognostic factors

The following patient and tumour characteristics were determined at time of primary diagnosis: patient's age, menopausal status, number of positive lymph nodes, number of lymph nodes examined, tumour size, tumour grade according to Bloom and Richardson [12] and oestrogen (ER) and progesterone receptor (PR) status. For the determination of nodal status an *en bloc* axillary dissection with at least six identifiable lymph nodes was performed. Tumour grade was centrally determined in a single histopathological reference centre. Hormone receptor status, both ER and PR, was measured biochemically by a dextran-coated charcoal method and classified as positive if the respective value was equal or greater than 20 fmol/mg. Quality control for the hormone receptor analysis was performed centrally.

2.4. 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 performed every 3 months during the first 2 years after operation, every 4 months during the following 3 years, every 6 months in years 6 and 7, and in annual intervals thereafter. Patients were followed until the middle of 1997 leading to a median follow-up time of approximately 8 years (range: 0.2–12.5 years). Not all patients followed the observation schedules planned in the study protocol. At the end of the observation period, documentation of follow-up visits was missing for several

patients. Therefore, information on the actual survival status of patients with incomplete follow-up was requested from the appropriate registry offices. This information was used for the calculation of overall survival and therefore increased the median follow up-time in this respect to approximately 10 years (range: 0.5–12.5 years). For calculation of time to recurrence, however, the last information available from the clinical centre was used.

Recurrence was defined as local (operation scar or chest wall), regional (axillary lymph nodes or supraclavicular region), or distant (metastases). Other events considered were second cancer (contralateral or at a distant site) and death without previous recurrence. The first event of failure was classified as isolated locoregional recurrence (appearance of local or regional recurrence at least 4 weeks before the diagnosis of distant failure or death), as distant failure (distant metastases or second cancer with or without a simultaneous locoregional recurrence), or death without recurrence. EFS was defined from mastectomy to the first event of recurrence or death without recurrence. OS was defined as the time from mastectomy to the patient's death from any cause.

2.5. Statistical methods

EFS and OS probabilities were estimated by the Kaplan–Meier method [13]. Simultaneous confidence bands for survival curves were calculated according to Hall and Wellner [14]. Event-specific rates for the first event of failure after mastectomy were estimated using the methodology of cumulative incidence rates [15]. To quantify the median follow-up time, the censoring distribution was estimated by the Kaplan–Meier method, also called 'reverse Kaplan–Meier' [16]. The effects of the following factors on EFS and OS were analysed: patient's age in years ($\leqslant 40$, 41–60, >60), menopausal status (pre, post), number of positive lymph nodes (10–15, $\geqslant 16$), number of lymph nodes examined (10–19, $\geqslant 20$), degree of lymph node involvement (all nodes examined are positive, not all nodes examined are positive), tumour size in mm ($\leqslant 30$, >30), tumour grade according to Bloom and Richardson [12] (I, II, III), ER and PR status measured as fmol/mg cytosol protein ($\geqslant 20$, <20). The relative risks between different groups defined by prognostic factors with corresponding 95% confidence intervals (CI) were determined by the Cox regression model [17]. *P* values were based on Wald tests [15]. The models were stratified for adjuvant treatment (CMF, CMF + tamoxifen, CMF + radiotherapy) in order to account for probable confounding by treatment. Since patients treated with three cycles of CMF had a comparable prognosis to patients treated with six cycles CMF [8], the duration of CMF chemotherapy was not used as a stratification criterion. The majority of the prognostic factors were classified as described in earlier analyses of the studies [7–9], the remaining factors were pre-defined independent of outcome. If a prognostic factor had been classified in more than two categories, it was coded using dummy variables in order to estimate the relative risks between the different categories separately. In multivariate models, only patients with complete data referring to the included factors were analysed (135 out of 141 patients). All data storage and analysis was performed using the Statistical Analysis System [18].

3. Results

The patient population comprised 141 patients with 10 or more positive axillary lymph nodes, who entered either GBSG trial 2 or 3 between 1984 and 1989. Patient characteristics are displayed in Table 1.

A median number of 13 positive lymph nodes was found (lower quartile = 11, upper quartile = 17). The median number of lymph nodes examined was 17. Since there was considerable variation in the number of lymph nodes examined (10% quantile = 11, lower quartile = 14, upper quartile = 22, 90% quantile = 27), we expressed the number of positive lymph nodes as a percentage of the number examined as a further characteristic of the degree of lymph node involvement. In 36 patients (26%) all lymph nodes examined were positive.

84 patients (60%) were treated by CMF chemotherapy alone as adjuvant systemic treatment. 37 patients (26%) received tamoxifen in addition to CMF, and 20 patients (14%) received CMF plus radiotherapy. Treatment assignment took place in a randomised manner for 87 patients (62%).

After a median follow-up time of approximately 8 years documented by the clinical centre, 110 events for the endpoint EFS have been observed. Fig. 1 shows the EFS rate. EFS was 22% (95% CI (14%, 29%)) after 5 years, and 14% (95% CI (7%, 21%)) after 10 years, respectively.

The first event of failure was an isolated locoregional recurrence in 35 patients, in 72 patients the first event of failure was a distant recurrence, and 3 patients died without a previous recurrence. The probability of developing an isolated locoregional recurrence as a first event within 10 years is estimated as 26% with a 95% CI of (19%, 35%), and the probability of developing distant failure as the first event within 10 years is estimated as 55% with a 95% CI of (46%, 64%).

With respect to the endpoint OS, the median follow-up time was approximately 10 years. During this time, 111 deaths were observed. Fig. 1 shows the overall survival rate. The OS rate was 39% (95% CI (31%, 47%)) after 5 years, and 19% (95% CI (12%, 26%)) after 10 years.

Table 2 shows the univariate analyses of the effects of prognostic factors on EFS and OS.

Regarding the factor age, there was a tendency for a better prognosis in the middle age group (41–60 years) compared with younger or older patients, but this effect was statistically non significant. With an increasing number of positive lymph nodes, the risk of recurrence or death was increased, which was significant with respect to EFS. Whereas the number of lymph nodes examined did not show a significant effect on EFS or OS, the number of positive nodes as a percentage of the number of nodes examined seemed to characterise the degree of lymph node involvement and showed a significant effect. With respect to EFS, the risk was estimated as increased by a factor of 1.57 (95% CI (1.0, 2.5)) when all nodes examined were positive compared with patients where one or more nodes were tumour-free. With respect to OS, the corresponding relative risk was estimated as 1.72 (95% CI (1.1, 2.7)).

Table 1
Description of patient population

Factor	Number of patients (%)
Age (years)	
⩽40	15 (11)
41–60	82 (58)
>60	44 (31)
Menopausal status	
Pre	55 (39)
Post	86 (61)
Number of positive lymph nodes	
10–11	50 (35)
12–15	39 (28)
⩾16	52 (37)
Number of lymph nodes examined	
10–15	49 (35)
16–19	46 (33)
⩾20	46 (33)
Degree of lymph node involvement	
<100% positive	105 (74)
=100% positive	36 (26)
Tumour size (mm)	
⩽20	19 (13)
21–30	57 (40)
>30	65 (46)
Tumour grade	
I	4 (3)
II	89 (63)
III	48 (34)
Oestrogen receptor (fmol/mg)	
⩾20	74 (53)
<20	65 (47)
Unknown	2
Progesterone receptor (fmol/mg)	
⩾20	59 (44)
<20	76 (56)
Unknown	6
Treatment	
CMF	84 (60)
CMF + tamoxifen	37 (26)
CMF + radiotherapy	20 (14)

CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

In the analysis of tumour grade, patients with grades I and II were combined in one group because there were only 4 patients with grade I tumour. The risk was estimated as increased by a factor of approximately 1.5 (95% CI (1.0, 2.3)) for patients with tumour grade III compared with patients with tumour grade I or II. The PR status shows a strong prognostic effect. With respect to EFS, the risk is increased by a factor of approximately 2 for PR-negative patients compared with PR-positive patients, and with respect to OS the corresponding relative risk is approximately 3. The ER status showed an effect on OS with an estimated relative risk of approximately 1.6.

Table 3 shows the result of a multivariate analysis of the prognostic factors which showed an effect on EFS or OS in the univariate analyses using the 5% level of significance.

The degree of nodal involvement still showed a slight effect, but this effect was not statistically significant in the multivariate analysis. The number of positive lymph nodes was associated with the risk of recurrence, the relative risk being 1.65 (95% CI (1.1, 2.5)) for patients with more than 15 positive lymph nodes compared with patients with 10–15 positive nodes. The effect on OS was non significant. The only factor showing a strong prognostic effect on both EFS and OS, was PR status. Even when adjusted for the other factors included, the relative risk of PR-negative tumours compared with PR-positive tumours was estimated as 2.32 (95% CI (1.4, 3.8)) with respect to EFS and as 3.13 (95% CI (1.9, 5.2)) with respect to OS. The effect of the ER status on OS, which was demonstrated in the univariate analysis, completely disappeared when it was adjusted for the PR status. The ER effect observed in the univariate analysis may be fully explained by the rather strong correlation of the ER and the PR status. In only approximately 25% of the patients the chosen negative/positive classification regarding the ER and PR receptor status produced discordant results. Therefore, an effect of the ER status was observed as long as the PR status was not adjusted for. This was also true in a multivariate analysis adjusted for nodal involvement and tumour grade (data not shown). Another correlation exists between tumour grade and ER and PR status, respectively. 66% (56%) of grade I or II tumours and only 29% (21%) of grade III tumours were ER (PR)-positive. Therefore, the effect of tumour grade is reduced when one of the receptors is included in the analysis. There is also a correlation between number of positive lymph nodes and degree of lymph node involvement such that the latter was not statistically significant if the number of positive lymph nodes was included in the model.

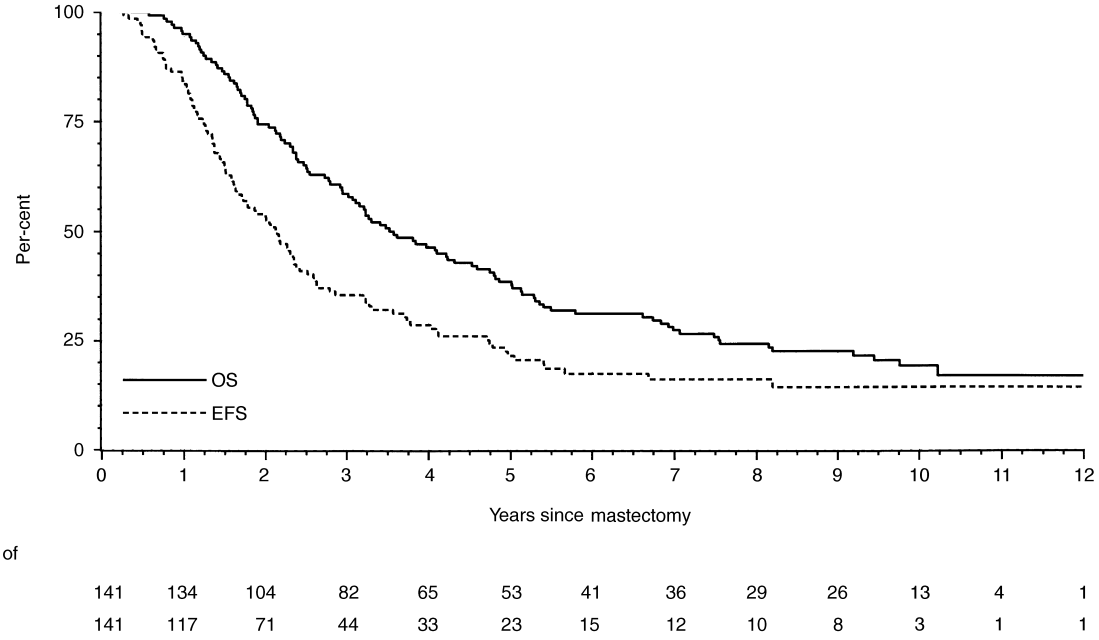

Fig. 1. Event-free survival rate (EFS) and overall survival rate (OS).

Table 2
Univariate analyses of effects of prognostic factors on event-free survival (EFS) and overall survival (OS) stratified for adjuvant treatment

Factor	Effect on EFS		Effect on OS	
	RR 95% CI	*P* value	RR 95% CI	*P* value
Age (years)				
⩽40	1.00	0.20	1.00	0.23
41–60	0.77 (0.4, 1.5)		0.72 (0.4, 1.3)	
>60	1.12 (0.6, 2.2)		1.01 (0.5, 1.9)	
Menopausal status				
Pre	1.00	0.40	1.00	0.28
Post	1.20 (0.8, 1.8)		1.26 (0.8, 1.9)	
Number of positive lymph nodes				
10–15	1.00	0.028	1.00	0.31
⩾16	1.54 (1.0, 2.3)		1.22 (0.8, 1.8)	
Number of lymph nodes examined				
10–19	1.00	0.64	1.00	0.44
⩾20	1.11 (0.7, 1.7)		1.18 (0.8, 1.8)	
Degree of lymph node involvement				
<100% positive	1.00	0.045	1.00	0.017
=100% positive	1.57 (1.0, 2.5)		1.72 (1.1, 2.7)	
Tumour size (mm)				
⩽30	1.00	0.63	1.00	0.17
>30	1.10 (0.7, 1.6)		1.31 (0.9, 1.9)	
Tumour grade				
I/II	1.00	0.045	1.00	0.042
III	1.52 (1.0, 2.3)		1.53 (1.0, 2.3)	
Oestrogen receptor (fmol/mg)				
⩾20	1.00	0.30	1.00	0.014
<20	1.23 (0.8, 1.8)		1.62 (1.1, 2.4)	
Progesterone receptor (fmol/mg)				
⩾20	1.00	0.0004	1.00	0.0001
<20	2.05 (1.4, 3.1)		3.03 (2.0, 4.6)	

RR, relative risk.

Table 3
Multivariate analyses of effects of prognostic factors on event-free survival (EFS) and overall survival (OS) stratified for adjuvant treatment (135 patients with complete data, 106 events for EFS, 106 events for OS)

Factor	Effect on EFS		Effect on OS	
	RR 95% CI	*P* value	RR 95% CI	*P* value
Number of positive lymph nodes				
10–15	1.00	0.016	1.00	0.30
⩾16	1.65 (1.1, 2.5)		1.24 (0.8, 1.9)	
Degree of lymph node involvement				
<100% positive	1.00	0.49	1.00	0.16
=100% positive	1.19 (0.7, 1.9)		1.41 (0.9, 2.3)	
Tumour grade				
I/II	1.00	0.39	1.00	0.99
III	1.23 (0.8, 2.0)		1.00 (0.6, 1.6)	
Oestrogen receptor (fmol/mg)				
⩾20	1.00	0.17	1.00	0.70
<20	0.71 (0.4, 1.2)		0.91 (0.6, 1.5)	
Progesterone receptor (fmol/mg)				
⩾20	1.00	0.0001	1.00	0.0001
< 20	2.32 (1.4, 3.8)		3.13 (1.9, 5.2)	

RR, relative risk.

In an additional analysis (data not shown in detail), we investigated the effect of the occurrence of an isolated locoregional recurrence (ILRR) on the overall survival time by adding a time-dependent covariate to the multivariate Cox model presented in Table 3. The risk of dying was estimated to be increased by a factor of 2.3 (95% CI (1.4, 3.7), $P=0.0011$) when an ILRR occurred, whereas the estimated relative risk for the other prognostic factors were similar to those given in Table 3. When differentiating between an ILRR occurring within 2 years after primary diagnosis and an ILRR occurring later, the estimated relative risks associated were 3.1 (95% CI (1.7, 5.5), $P=0.0001$) and 1.3 (95% CI (0.5 , 3.0), $P=0.59$), respectively.

4. Discussion

Here, we presented the long-term prognosis of breast cancer patients with 10 or more positive lymph nodes treated with a standardised, conventional dose CMF chemotherapy within two prospective studies. Existing treatment heterogeneity with respect to additional hormonal treatment or radiotherapy has been accounted for by stratification. There are only a few studies with a sufficient number of patients included and/or a long-term follow-up in this high-risk group [2,3,19–21] although the poor prognosis of these patients requires improvement [22].

We investigated the effects of various standard prognostic factors which had been prospectively collected in this study. In univariate analyses, the number of positive lymph nodes, the degree of lymph node involvement, tumour grade, ER and PR status showed a significant effect on EFS or OS. In a multivariate analysis, PR status remained the only statistically significant predictor for both, EFS and OS. The univariate effect of ER status may be explained by its strong correlation to PR status. It should be noted, however, that ER status would also be a significant predictor if PR status is excluded from the multivariate model. The effect of PR status appeared to be rather strong in terms of the estimated relative risks (2.32 for EFS and 3.13 for OS, respectively). This is translated into OS rates for PR-positive patients of 0.64 (95% CI (0.51, 0.76)) after 5 years and of 0.26 (95% CI (0.13, 0.40)) after 10 years. The corresponding rates for PR-negative patients were 0.17 (95% CI (0.09, 0.26)) after 5 years and 0.11 (95% CI (0.04, 0.19)) after 10 years. In summary, we found a rather large prognostic variability even in this high-risk patients with 10 or more positive lymph nodes. Interestingly, the occurrence of an ILRR has a strong prognostic effect on subsequent survival in this patient population, the effects observed being only somewhat smaller in magnitude than in node-negative and node-positive breast cancer patients in general [23].

One of the referees of this paper questioned whether our patient group is representative because, according to the study protocols, only the examination of six lymph nodes was required. We expect, however, the number of patients falsely not diagnosed as having 10 or more positive nodes to be rather small since, for the vast majority of the study patients (78%), 10 or more lymph nodes had been examined. Furthermore, our main goal was the investigation of the effects of prognostic factors, i.e. relative comparisons within this group, which are not expected to be affected by this point.

The effect of prognostic factors in this patient population have also been looked at by other authors. Buzzoni and colleagues [2] investigated the effect of a variety of factors in their randomised trial comparing two different conventional dose chemotherapeutic regimens, but concentrated on multiple treatment comparisons in various prognostic subgroups. From their results [2], it can be derived, however, that there was at least a univariate prognostic effect of both ER and PR status on EFS. It must be taken into account that their trial was open for patients with more than three positive nodes, only one-third of them ($N=121$) having more than 10 positive nodes. Gianni and colleagues [19] performed a multivariate analysis of their series of patients, who were treated with high-dose chemotherapy ($N=67$) in comparison to a cohort of historical controls, treated with conventional dose chemotherapy ($N=58$). They looked at various prognostic factors, including ER and PR status. Unfortunately, they only reported that, ''From this analysis, high-dose therapy emerged as the most important factor influencing the relapse rate,'' without mentioning anything about the effects of the other factors examined.

In a case series of 114 patients, treated with two regimens of high-dose chemotherapy, Somlo and colleagues [21] performed a comprehensive analysis of prognostic factors. In univariate analyses, ER and PR status, as well as tumour grade, were significant factors for OS; in a multivariate analysis only PR status appeared to be a significant predictor for OS. From their data it can be derived that the estimated effect size was of a similar magnitude as the one observed in our study. It should be noted, however, that in their study, in contrast to ours, only one-third were stage II patients, the others being stage IIIa or IIIb.

In a recent paper, Mikhak [24] presented the results of a study with 64 patients with 10 or more positive lymph nodes all being treated with conventional dose chemotherapy. In a univariate, as well as in a multivariate, analysis investigating various prognostic factors, including ER and PR status, they failed to identify any significant predictor for both EFS and OS. In another study, recently published by Moore and colleagues [25], the role of various prognostic factors was examined in a series of 103 patients treated with high-dose chemotherapy and additional radiotherapy, 82% having 10 or more positive lymph nodes. They found a statistically significant effect of the ER as well as the PR status in the univariate analyses presented. A multivariate analysis was not performed. In other reports, the ER and PR status was either not investigated [26], or not considered in the statistical analysis [27,28]. In some, the missing rates of ER and PR status were so high that the results must be judged as inconclusive [3,20,29].

In conclusion, there is some corroborating data in the literature that the PR status may indeed be considered as a strong predictor in the high-risk group investigated. The fact that Mikhak and colleagues [24] failed to observe a significant effect may be explained by the insufficient power of that study. It is well known that the power for testing a binary factor in a prognostic factor study depends on the factor's prevalence and the number of events observed [30]. In the study of Mikhak and colleagues [24], the prevalence of PR-positive patients was 64% and the number of deaths was 37, whereas in our study the corresponding figures were 44% and 111, respectively. Therefore, the power of Mikhak and colleagues [24] study to identify a binary factor associated with a true relative risk of 1.5 is 0.23, in contrast to 0.56 in our study. For a larger effect corresponding to a relative risk of 2 the power is calculated as 0.53 and 0.95, respectively. Thus the study by Mikhak and colleagues [24] only has sufficient power to be able to identify prognostic factors associated with very large effects. Our study, however, has sufficient power to identify prognostic factors exhibiting even moderate effects.

Treatment has been given in a standardised manner, hereby meeting one of the important prerequisites of a prognostic study [31]. All patients received conventional CMF chemotherapy, subgroups were treated with radiotherapy or hormonal therapy in addition. It has to be admitted, however, that meanwhile other chemotherapeutic regimens are used in this high-risk group of patients, mostly doxorubicin-containing regimens [2,3,21] or high-dose chemotherapy combined with autologous bone marrow [32] or stem cell transplantation [25,29]. Current knowledge indicates that these new regimens may lead to a slight improvement in the OS of these patients. This assumption, however, is mostly based on results of case series with patients who underwent a selection process [4,20,33]. It is unlikely that a treatment effect is as large as, for example, the prognostic effect of the progesterone receptor status observed in this and in other studies [2,21,25]. Consequently, positive results in patients selected from such a heterogeneous patient population have always to be considered as possibly resulting from selection [4].

It was not the aim of this analysis, which combined randomised and non-randomised patients from two studies, to investigate treatment effects. These results have already been reported [8,9]. However, the analysis of prognostic factors presented here was stratified for treatment, in order to account for probable confounding.

To put the results of the presented and other studies into perspective we display the reported overall survival rates in this high risk group of breast cancer patients in Fig. 2.

Also included are the studies presented at ASCO 1999 [34,35] excluding the South African Study [36] because of the subsequent irregularities that were found [37]. It is obvious that the results of most studies or study arms

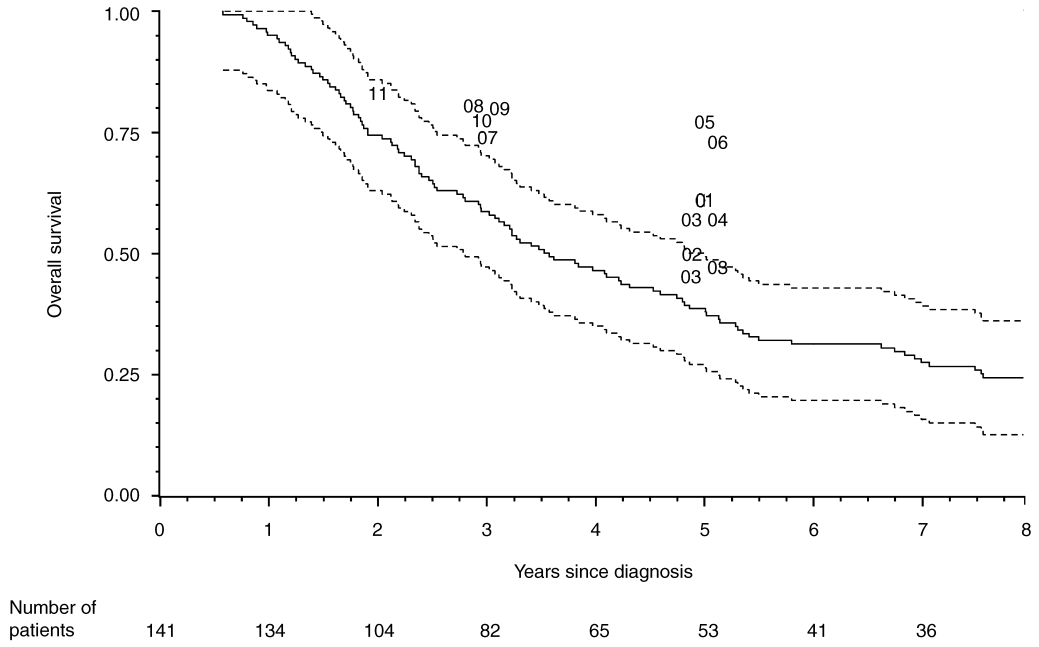

Fig. 2. Observed overall survival (OS) rate with 95% confidence band in GBSG studies and results in this high-risk group reported in the literature after conventional dose chemotherapy (CD) and high-dose chemotherapy (HD): 01 [19] CD, 02 [20] CD, 03 [32] CD (several control groups), 04 [24] CD, 05 [19] HD, 06 [32] HD, 07 [38] HD, 08 [29] CD + HD, 09 [34] CD, 10 [34] HD, 11 [35] CD + HD.

using conventional dose chemotherapy as treatment (CD) [19,20,24,32] were close to the survival curve that we observed in our study. One of the exceptions is the study of Gianni and colleagues [19], which showed a better survival rate. This may be due to the fact that the series with the best result they ever achieved in their institution by conventional dose chemotherapy was chosen as the control group. The results of the case series treated with high-dose chemotherapy (HD) [19,32,38] are markedly better, having led to the optimistic assessment of that therapy in the past [4]. The preliminary results of the three randomised trials [29,34,35] comparing high-dose with conventional dose chemotherapy, are somewhat better than the results of our study, but are similar for both arms. This may be interpreted as an indication for underlying selection mechanisms in these studies that can only be controlled by randomisation [4,20,33].

In order to improve the prognosis of these high-risk breast cancer patients by new treatment modalities, randomised trials of high quality are needed and the information on prognostic factors should be incorporated [39,40], especially the PR status should be taken into account in the design and analysis.

Acknowledgements

This study was sponsored by the Bundesministerium für Forschung und Technologie (BMFT) and by the Deutsche Forschungsgemeinschaft (DFG).

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