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RESEARCH

Inflammatory Breast Cancer—Comparing the Effectivity of Preoperative Docetaxel-Epirubicine Protocol to Conventional Antracycline-Containing Chemotherapy to Achieve Clinical Benefit and Complete Pathological Response

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Abstract Our retrospective analysis compared the effectiveness of conventional antracycline-containing protocols (A+) and docetaxel/epirubicine (TE) as primary systemic chemotherapies (PSCT) for inflammatory breast cancer (IBC). Seventy IBC patients received either A+(n=48) or TE (n=22) as PSCT. The objective clinical response and clinical benefit rate of treated patients were 54.3% (A+: 54,2% vs. TE: 54,5%; p=0,28) and 92.8% (A+: 91,7% vs. TE: 95,5%; p=0,57), respectively. The clinical complete response rate (cCR) was 23.2% (A+: 27,1% vs. TE:4,5%; χ^2=4,79; p=0,03) with 7.14% (A+: 10,4% vs. TE:0%; χ^2= 2,47; p=0,12) of pathological complete responses (pCR). The median progression free (PFS)/local progression free (LPFS)/overall survival (OS) was 2.0/5.4/4.0 years, respectively. Patients achieving cCR had a tendency for better survival parameters than patients with less than cCR. Response rates or survival data were not statistically different in the two chemotherapy (CT) treatment groups. The survival was not influenced by the number of CT cycles in either protocols. In this set of patients, the clinical efficacy of the two alternative primary systemic chemotherapies (A+and TE) is equivalent in the treatment of inflammatory breast cancer (IBC), despite of the significant difference in favour of A+noticed in CRs. Six cycles of CT could be enough for patients achieving CR, however sequential pre- and/or postoperative CT with non cross-resistant drugs should be considered for non-responders.

Keywords Anthracycline · Docetaxel · Inflammatory breast cancer · Pathological complete remission · Primary systemic chemotherapy

Abbreviations

IBC	Inflammatory breast cancer
BC	Breast cancer
LABC	Locally advanced breast cancer
PSCT	Primary systemic chemotherapy
CT	Chemotherapy
ST	Surgical treatment

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RT	Radiotherapy
ET	Endocrine therapy
T	Docetaxel
TE	Docetaxel-epirubicine protocol
A+	Conventional second generation antracycline containing chemotherapy
TAC	Docetaxel—doxorubicine—cyclophosphamide protocol
cCR	Clinical complete remission
pCR	Pathological complete remission
PR	Partial remission
SD	Stable disease
PD	Progressive disease
PFS	Progression free survival
LPFS	Local progression free survival
OS	Overall survival
RR	Response rate
C.I	Confidence interval
DLI	Dermal lymphatic involvement
US	Ultrasound
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
NIH	National Institute of Health
NCCN	National Comprehensive Cancer Network
UICC	International Union Against Cancer

Introduction

Inflammatory breast cancer is the most aggressive form of BCs comprising 1–6% of all invasive BC cases [1, 2]. The incidence (0,7/100.000) of IBC is growing more rapidly comparing to the non-inflammatory form of BC [3, 4].

Consistently with Haagensen's original description of IBC [5], the American Joint Committee on Cancer (AJCC) provides the current definition for this form of BC, describing it as both a clinical and a pathologic entity that is characterized by diffuse erythema affecting at least one-third of the underlying skin and often without an underlying palpable mass. Edema (peau d'orange) affecting at least two-third of the breast, induration (often without border), touchiness and warmth can also be detected. The nipple usually gets flattened or inverted. The development of clinical signs and symptoms of IBC is always fulminant: usually it takes less than 3 months. Palpable axillary lymph node enlargement can be found in most of the patients and distant metastases can be detected in one-third of the cases at the time of diagnosis. The diagnosis of IBC is based on clinical symptoms rather than the pathological confirmation of dermal lymphatic invasion (DLI) [6]. IBC usually associated with high-grade invasive ductal carcinoma with peritumoral lymphatic invasion, extensive angiogenic signs and hormone receptor negativity [7].

The multidisciplinary management of IBC includes PSCT, and surgery (ST), radiotherapy (RT) and—in case of hormone receptor positivity—endocrine therapy (ET). In HER2/neu positive disease trastuzumab therapy has already been tested (e.g. [8, 9]). The addition of neoadjuvant and adjuvant trastuzumab to neoadjuvant chemotherapy should be considered for women with HER2-positive locally advanced or inflammatory breast cancer to improve event-free survival, survival, and clinical and pathological tumour responses.. Postoperative adjuvant treatments are based on postoperative histological parameters according to well-accepted guidelines (NIH, NCCN, St. Gallen Consensus).

The length and components of PSCT are basically defined. Adding a taxane to an anthracycline-containing regimen further improved the DFS in most of the neo-adjuvant and adjuvant trials. However there is a large degree of heterogenity in evidences regarding the effectiveness of taxane-containing regimens compared to non-taxane-containing protocols in terms of interventions, comparators and populations [10]. There are only few data available *specifically* for the PSCT of IBC. In our retrospective case controlled study we compared the clinical efficacy of conventional non-taxane based, A+ protocols with the TE combination in inflammatory breast cancer patients.

Patients and Methods

Patients and Diagnostic Work-Up

Clinical records of 74 IBC patients referred to the Multidisciplinary Breast Cancer Consulting Committee of the National Institute of Oncology between 1.1.1997 and 31.12.2004 were analyzed retrospectively. The diagnosis of IBC had been set up according to Haagensen's criteria, so by definition IBC means a cT4d breast cancer (UICC TNM 6.0). Beyond physical examination, mammography and complex breast examination utilizing ultrasonography and more recently MRI, evaluations of primary tumors and presurgical clinical responses were performed by aspiration cytologies and/or core biopsies as well. Before starting any PSCT, irresecability of tumors had to be confirmed.

Response Evaluation

Clinical response evaluation with imaging methods usually was performed after the 4th–6th cycles of PSCT. For the improvement of local control, preoperative radiotherapy could be applied after PSCT by the physician's individual decision. If resecability was achieved, surgery and—

depending on the histological findings—adjuvant chemo-, radio- and endocrine therapies were also applied.

Treatment and Follow-Up

In case of the evaluable 70 patients the following PSCT protocols were used: 6–8 cycles of FAC/FEC (500 mg/m2 5-fluorouracil (5-FU), 50 mg/m2 doxorubicine or 70–75 mg/m2 epirubicine and 500 mg/m2 cyclophosphamide, d1 q3w) or AC (60 mg/m2 doxorubicine and 600 mg/m2 cyclophosphamide, d1 q3w), 6 cycles of CEF (500 mg/m2 5-FU, 70–75 mg/m2 epirubicine and 500 mg/m2 cyclophosphamide, d1,8 q4w); and 4 cycles of TE (75 mg/m2 docetaxel and 75 mg/m2 epirubicine, d1 q3w). Four non-evaluated patients received docetaxel-carboplatin, and CMF treatments.

In case of hormone receptor positivity (defined by ER and/or PR immunhistochemical positivity≥10%) the appropriate endocrine treatments (ET) were used postoperatively (N=42) for 5 years. If case of HER2 positivity (confirmed by IHC or FISH), adjuvant trastuzumab was given for 1 year (n=6).

In the preoperative setting loco-regional radiotherapy (RT) consisted of whole breast irradiation using paralell opposed tangential 6–9 MV photon beams matched with an AP supraclavicular-axillary 6–9 MV photon beam up to a total dose of 50–50 Gy with conventional fractionation (2 Gy/day, 5 fractions/week). A boost dose of 10 to 20 Gy was given to the tumour bed using 6–18 MeV direct electron beams. The same technique and doses were applied in the postoperative setting for patients treated with breast-conserving surgery (n=2) after neoadjuvant chemotherapy. After mastectomy the chest-wall was irradiated via tangential 6–9 MV photon or direct 6–12 MeV electron fields matched with an AP supraclavicular-axillary 6–9 MV photon field up to a total dose of 50–50 Gy using conventional fractionation. No boost dose was given to the chest-wall. For patients with clinically or pathologically positive axillary nodes and central or inner quadrant lesions or with radiographic evidence of positive internal mammary nodes, treatment of the internal mammary nodes were administered either with deep tangents or mixed photons and electrons. A CT-based treatment planning was used for all patients.

In Table 1. we summarized the main patient, disease and treatment characteristics.

Table 1 Summary of main patient and disease characteristics

Patients:	
Age at time of diagnosis (average±S.D. [range]):	57.38±11.4 [27.5–77.0] year
Menopausal status:	
Premenopausal	25.71%
Perimenopausal	2.86%
Postmenopausal	71.43%
Median time to first perception of breast mass to diagnosis	6.0 months
Median time from diagnosis to start PSCT	22.3 days
Visible tumor sizes	
Mammography	40.2±33.6 mm
Ultrasound	30.8±24.7 mm
Physical examination	56.53±32.1 mm

Evaluation and Statistical Methods

To determine the efficacy of PSCT, we analyzed the clinical therapeutic responses, histological result of surgery, and different survival parameters. Determination of clinical responses before surgery was primary based on observations of oncologists' and the surgeons', based on the physical examination and imaging results. Complete clinical remission (cCR) was recorded if any signs or symptoms of IBC have disappeared by both physical examination and on the imaging studies. Progressive disease (PD) was considered if the disease progressed according to the description of signs and symptoms or imaging studies or when the preexisting tumor diameter became 25% larger. Clinical partial response (cPR) was defined by the clear, greater than 50% remission in diameter of the primary tumor with the concomitant achievement of resecability. Cases falling between cPR and PD were considered as stable disease (SD) irrespectively from achieving resecability or not. In cases showing irresolvable discrepancies between results of physical evaluation and the imaging results, we accepted the *worse* clinical result category. After surgery was performed complete pathological response (pCR) was stated if both the invasive and non-invasive parts of the tumor have been completely disappeared from the breast and the lymph nodes. This corresponds to regression grade 5 according to the modified regression grading system described by Sinn et al. [11, 12].

Overall survival (OS) was defined as time from starting PSCT until death from any cause. Censoring time for living patients was 01.09.2008. or the last contact closest to this date. Progression-free survival (PFS) was defined as time from starting PSCT to first loco-regional or distant progression of breast cancer, second primary breast cancer or death from any cause. Local-regional recurrence was defined as ipsilateral disease recurring at the chest wall close to surgical scar, axilla and/or supraclavicular-parasternal region. Time to locoregional progression, named LPFS, was defined as time from starting chemotherapy to first local recurrence of breast cancer in the mentioned areas.

Statistical analyses were conducted with using *Statistica® 7.1* software (StatSoft® Inc., Tulsa, OK, USA). Descriptive

Table 2 Distribution of the pre-operative stage, main histopathologic features, receptor status and treatments between the two arms

		Anthracycline (*N*=48) N/all%	TE (*N*=22) N/all%	p
Axillary nodal status (cN)[a]	cN0	9/12.9%	5/7.1%	0.75
	cN1	23/32.9%	9/12.9%	0.39
	cN2	16/22.9%	8/11.4%	0.5
Clinical stage	III/B (T4, N0-2)	44/62.9%	21/30.0%	0.5
	III/C (any T, N3)	4/5.7%	1/1.4%	
Histology from core biopsy	Invasive ductal	14/43.8%	11/34.4%	0.1
	Invasive lobular	0/0.0%	3/9.4%	0.12
	Invasive apocrin	1/3.1%	1/3.1%	0.74
	No tumor (fibrosis)	1/3.1%	1/3.1%	0.52
Histological grade	I	0/0.0%	1/3.5%	0.5
	II	3/10.3%	6/20.7%	0.21
	III	12/41.4%	7/24.1%	0.12
Hormone receptor status[b]	negative	2/6.3%	8/25.0%	0.027
	positive	14/43.8%	8/25.0%	
HER2[c]	negative	10/35.7%	11/39.3%	0.45
	positive	3/10.7%	4/14.3%	
Treatments:	preoperative irradiation	13/18.6	9/12.9	0.19
	adjuvant chemotherapy	22/31.4	15/21.4	0.07
	adjuvant irradiation	21/30.0%	9/12.9%	0.52
	adjuvant endocrine therapy[d]	30/62.5%	12/54.5%	0.35
	adjuvant trastuzumab treatment	4/5.7%	0/0%	0.21

[a] palpable supraclavicular lymph node (cT3c) 4 (5,71%)

[b] one and [c] two of them from cytology

[d] based on pre- and postoperative hormonereceptor results

statistics for characterize variables and matched pair tests were performed. Univariate analysis was used for describing the difference between two proportions for qualitative data (Pearson's χ^2-test). (In case of small sample size we used the results of Fischer's exact test or the Yates-corrected χ^2-test.) For quantitative data we used Wilcoxon's rank sum test. Non-parametric comparisons between two groups were made with Mann–Whitney *U*-test. Continuously measured parameters were compared using the Kruskal-Wallis test. Three-year PFS, LPFS, and OS were calculated from the first day of the primary chemotherapy and were estimated by using the Kaplan-Meier method. Between-group comparisons were performed by log-rank test. In all statistics α was accepted to 0,05, 95% c.i.s were calculated.

Results

In Table 2. we provide relevant initial staging, histopathological findings and treatments of our patients. Palpable supraclavicular lymph nodes (cT3c) have been found in 4 patients (5.7%). Core biopsy was performed in 32 cases (45.7%). Due to the fragmentation of the specimen or the absence of tumor it was not possible to determine the

Table 3 Results in patients achieved cCR (*N*=17)

Not operated	3
Pathological CR	4 [+1][a] (7,14%)
Partial response	9
Stable disease	1
Histology unavailable (but presence of tumor confirmed)	2
Histology available:	
DCIS	2
Invasive ductal carcinoma	3[b]
Invasive mucinosus carcinoma	1
Inflammatory breast cancer	1
pCR, but lymph node metastasis	1

[a] one patient with clinically SD became pCR

[b] one only microscopic in size

Table 4 Clinical and pathological responses according to the PSCTs

	Clinical Response				Pathological Response			
	A+/%	TE/%	χ^2	p	A+/%	TE/%	χ^2	p
cCR/pCR	13/27.1	1/4,5	4.79	0.03	5/10.4	0/0	2.47	0.12
Major response (CR+PR)	26/54.2	12/54,5	1.16	0.28	23/47.9	9/40.9	0.15	0.70
Clinical benefit (CR+PR+SD)	44/91.7	21/95,5	0.33	0.57	44/91.7	21/95.9	0.33	0.59
All	48/100	22/100			48/100	22/100		

histological grade in 3 cases and the HER2/neu status in 4 cases. Significantly more hormone receptor negative patients were detected between TE treated patients.

Comparisons of Imaging Studies

The median time to first perception of palpable breast mass to diagnosis was 6 months; the median time to diagnosis to start PCT was 22.3 days. Diagnoses of IBC were based solely on clinical/radiological examinations in 57.1% (n=40) or pathological examination in 42.9% (n=30) as well. Visible tumor diameters measured by mammography (40.2±33.6 mm) and US (30.8±24.7 mm) were significantly correlated (r=0.64; p>0.001). Tumor diameters defined by physical examinations (56.5±32.1 mm) were also correlated significantly with mammography (r=0.59; p>0.003) or US (r=0.47; p=0.02) results.

Effectivity of PSCT in Terms of Responses

The objective RR was 56.8% with the clinical benefit (at least SD) of 92.9%. Clinical complete remission (cCR) was shown in 17 patients (24.3%). Results of histological evaluations of cCR and pCR patients are provided on Table 3. Detailed results comparing the two types of PSCT can be seen on Table. 4.

Clinical CR rate of patients receiving A+was significantly better, however the objective RR and the clinical benefit were not different. Although, we cannot demonstrate any significant difference between the two treatment groups in major response and pathological results, it is notably, that 5 pCRs were seen on the non-taxane arm vs nil on the TE arm. Response rates in all cases were inferior according to time to first perception of tumor to diagnosis (R=0.35; p=0.003), to histological grade (HG II vs III: Z=2.29; p=0.01), to progesterone receptor status (negative vs positive: Z=2.15; p=0.05), to both hormone receptor staining frequency: ER% (R=0.55; p=0.0001) and PR% (R=0.37; p=0.03) and marginally to HER2 status (negative vs positive: Z=1.98; p=0.07). However, between group comparisons revealed that only progesterone receptor status was significantly more positive (F=14.0, p=0.002) in the TE group.

The toxicity profile of these regimens are well known, and basically not really important in the decision making process. However, we did not observed more frequent or more severe side effects, as it has already been described.

Effectivity of PSCT in Terms of Survival Parameters

Survival parameters were inferior in greater tumors, lymph node positivity, higher grade, hormone receptor negativity, HER2 positivity, absence of necrosis in tumor, progesterone receptor negativity. In case of pCR, the fact of ST and RT, survival parameters were better in univariate analysis. No meaningful multivariate analysis can be performed due to the small number of cases.

After an average of 2.6±2.4 [0.16–10.0] years of follow-up 50% (n=35) of the patients was alive, and 32.9% (n=23) of the entire population was free of disease. Distribution of disease and survival status was presented in Table 5.

For the entire population the median PFS was 1.9 year, the median LPFS was 5.4 years, and the median OS was 4.0 years. Detailed survival data are shown on Table 5.

Patients achieved cCR had a tendency for longer survival parameters comparing to PR-SD patients, with a

Table 5 Disease and survival status at censoring time

Status: N=70	Cause	N/%	Cumulative	Alive at censoring N/%
Survival, no progression	–		23/32.9	23/32.9
Survival, progression	Locoregional	19/27.1	47/67.1	12/17.1
	Distant	22/31.4		
	Locoregion.+Distant	6/8.6		
Death	BC	21/31.4	35/50.0	–
	Cerebral hemorrhage[a]	1/1.4		

[b] without BC

median PFS of 3.7 vs. 1.9 years (p=0.41); with a not reached median LPFS vs. 5.0 years (p=0.44) and with an OS of 5.5 vs. 5.0 years (p=0.79).

In terms of PFS and OS but not in LPFS, a clear survival advantage was demonstrated for patients who achieved pCR. Survival curves are shown on Fig. 1.

We could not demonstrate any difference between the two types of PSCT in terms of survivals. Although the 3-year PFS/LPFS rates were somewhat higher with the conventional A+protocols, this was not significant and the reverse effect was detected on the OS.

At the censoring time, proportion of patients *dead or alive* (A:17/31 vs. TE: 5/17; χ^2=1.13; p=0.29), and *without BC or relapsed* (A:15/33 vs. TE: 8/14; χ^2=0.18; p=0.67) was not different. There was no type of comparisons which demonstrated any significant difference between the two types of PSCT. Similarly, median overall survival and 3 year survival rates (see Table 6. and Fig. 2.) were identical in both arms.

Effect of PSCT Cycles Given on Survival Parameters

Most patient were treated with 6 cycles of PSCT (n=48, 68.6%,), 10.0% (n=7) got 3 cycles, 17.1% (n=12) received 4-5 cycles, and 4.3% (n=3) had more than 6 cycles. In terms of all pre- and postoperative cycles proportion of patients received less, than 6 cycles was 7.1% (n=5), 6 cycles: 47.1% (n=33); 7-8 cycles: 30.0% (n=21); more than 8 cycles: 15.7% (n=15.7). Survival parameters (PFS, LPFS, OS) were not significantly different between groups. However those, who treated with less than 6 pre- *and* postoperative cycles seems to have somewhat worse survival parameters, than those who had 6 cycles or more: PFS: χ^2=5.28, p=0.15; LPFS: χ^2=1.15, p=0.77; OS: χ^2=4.01, p=0.26.

Discussion

Definition of pathological complete response is considered to a well-known problem in comparing different studies. In our study we use the strictest definition of pCR [11, 13] which explains a shift of the proportions of patients from CR to PR within ORR, and to SD from ORR can be seen. However, it is still problematic to define PR and SD, when results of physical examination and imaging are different. In our study, significant difference (approximately 2 cm) could be detected between physical examination and imaging studies; i.e. it is great enough for changing the actual stage definition of the remaining tumor! After taking into account the pathological measures in evaluating the therapeutic response 21.4% (15/70) of the results had to be changed! The same difference can be noticed in the GeparTrio trial, where 10–15% difference was reported

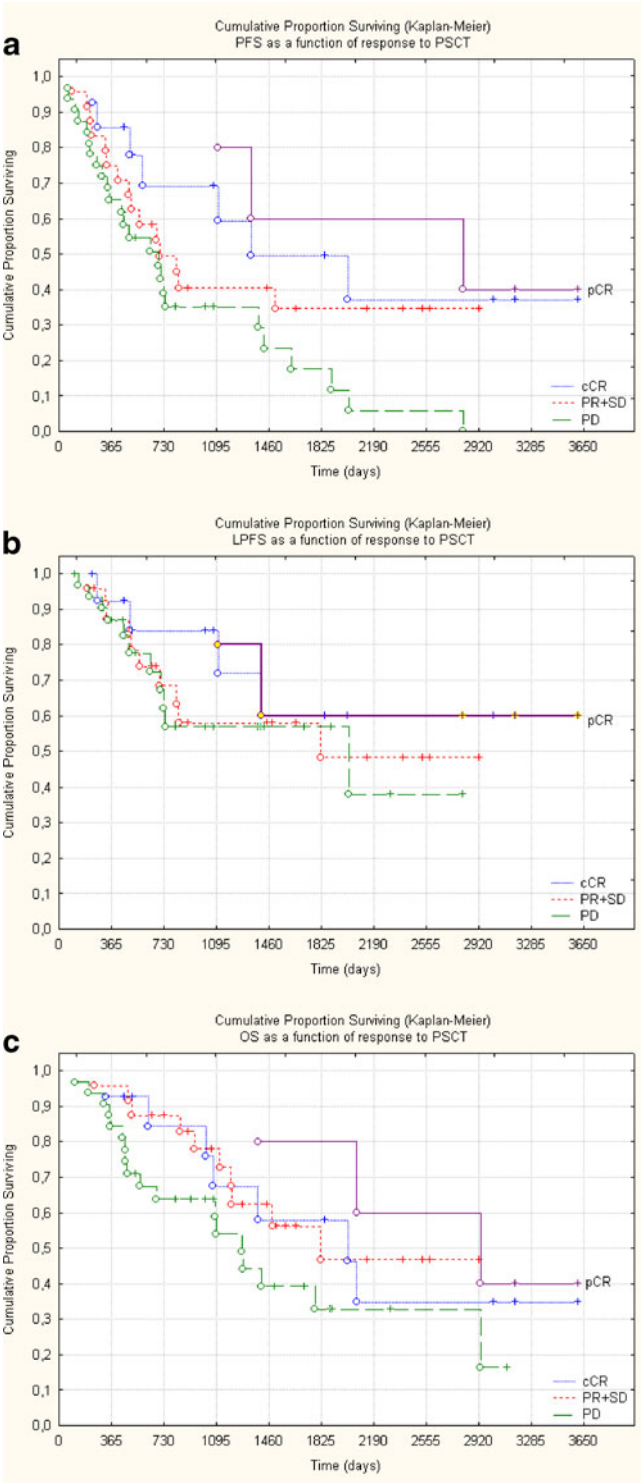

Fig. 1 Kaplan-Meier survival curves: According to clinical response after PSCT-**a** PFS; **b** LPFS; **c** OS (N=70); Note: Comparing cCR vs PR+SD: PFS Z=1.11 (p=0.27); LPFS Z=0.83 (p=0.41); OS Z=-0.09 (p=0.93); Note: *Solid line* indicates pCR

Table 6 Survivals as a function of type of PSCT

	Median survival				3 y survival			
Type of chemotherapy	N	PFS y	LPFS y	OS y		PFS%	LPFS%	OS%
Anthracycline-(non-taxane) combination	48	2.28	5.53	4.07		47.1	65.5	60.9
Docetaxel+epirubicine	22	1.99	not yet achieved	3.86		36.4	57.5	74.8
Log-rank p		0.13	−0.53	−0.39	HR	1.30	1.06	0.76
		0.90	0.60	0.7	(C.I.± 95%)	(0.18–2.42)	(0.08–2.04)	(0.34–1.19)

between the overall responses measured by US and physical examination at non-responding patient [12], and the difference was approximately doubled at the responding patients. Further refining the evaluation rules, introducing new imaging techniques (PET-CT) with tempering the subjective considerations could make a step forward in this sensitive field, which can determine the validity of all clinical studies in the field of LABC.

The problem of the clinical response evaluation is reflected in the observed difference in cCR and pCR. We found, that cCR approximately three-fold higher, than pCR in our patient population, that may reflects the definition of pCR. Other studies demonstrated less (approximately 1,5-2-fold) [14–16], or the same [17] differences. The median survival of patients achieved pCR is one year longer than patients reaching only cCR. Achieving pCR with PSCT is a direct and quick measure of sensitivity to chemotherapy. A positive correlation could be seen between response to PSCT in combination with multimodal approach and survival, CR patients would have significantly better long-term survival than others. [18–26]. One group described 87% 5 year DFS-t and 89% 5 year OS in CR patients having histologically negative breast and axilla after PSCT [18]. However, it seems to be quite provoking, that longer DFS and OS after achieving pCR may reflect a disease with better prognosis and an indolent course, but not necessarily a better sensitivity to chemotherapy [27].

Introduction of doxorubicin-based chemotherapy significantly improved results in IBC [28]. Three cycles of CAF or CEF followed by surgery, adjuvant chemotherapy and adjuvant irradiation also found to be equivalent in ORR, 5 and 10 year DFS and OS. [27] More intense chemotherapeutical protocols showed a significant improvement in both local relapse-free survival and breast cancer specific survival compared to AC/MF or FAC [26].

In a large series of MD Anderson's retrospective analysis taxane-containing regimens produced higher pCR rates compared to 3–4 cycles of A+. Here, the prognostic value of pCR was independent from type of the used chemotherapy and from the ER status [25]. Integrating sequential paclitaxel to an A+resulted significantly higher pCR, median PFS and median OS [16, 29]., The sequential A+ followed by adjuvant T improved RR and pCR rate compared to A alone [30], but, in contrast, concomitant T and A in the neoadjuvant setting failed to improve efficacy [31]. In the NSABP B-27 trial [32] adding sequential T to AC did not significantly affect OS, slightly improved DFS and decreased the incidence of local recurrences on stage II–III patients. Moreover, the improvement of pCR rate using second generation taxane-containing protocols did not turned to clinically meaningful improvements in long-term outcomes on operable patients. [33] Changing 5FU to T (i.e. TEC vs FEC) in the third generation concomitant protocol, however, showed further significant improvement in the neoadjuvant therapy of operable breast cancer.[34] More cycles of chemotherapy was an independent predictor of pCR in their and others series [35]. Opposing these results, in terms of pCR eight cycles of TAC was not significantly better than six cycles, but the majority of these patients has not IBC [12].

Comparing the taxane non-containing protocols to concomitant TE protocol in our study response rates and survival data were equivalent and analogous with results of these and other [36, 37] groups. We could also confirm, that achieving pCR renders a greater probability of longer PFS and LPFS, but not significant tendency in OS data. There is no clear explanation for the significant difference observed between the two treatment groups in cCR/pCR. One meaningful difference detected between the two treatment groups was the higher PR content in TE group. The anti-apoptotic effect of PR is documented. In their study, Schmidt et al. revealed that PR-rich tumors have decreased chemosensitivity to paclitaxel [38]. PR-A-rich tumors have heightened aggressiveness, and that abnormal PR-A excess is found in the healthy breasts of women with *BRCA1/2* mutations.[39] If so, these results along with others could be hypothesis-generating that needs to be confirmed in larger studies.

In one study for improving clinical results and resecability paclitaxel were used after initial PSCT for SD and PD patients and finally they were able to perform mastectomy on 7 of 16 patients [29]. *The practice in which*

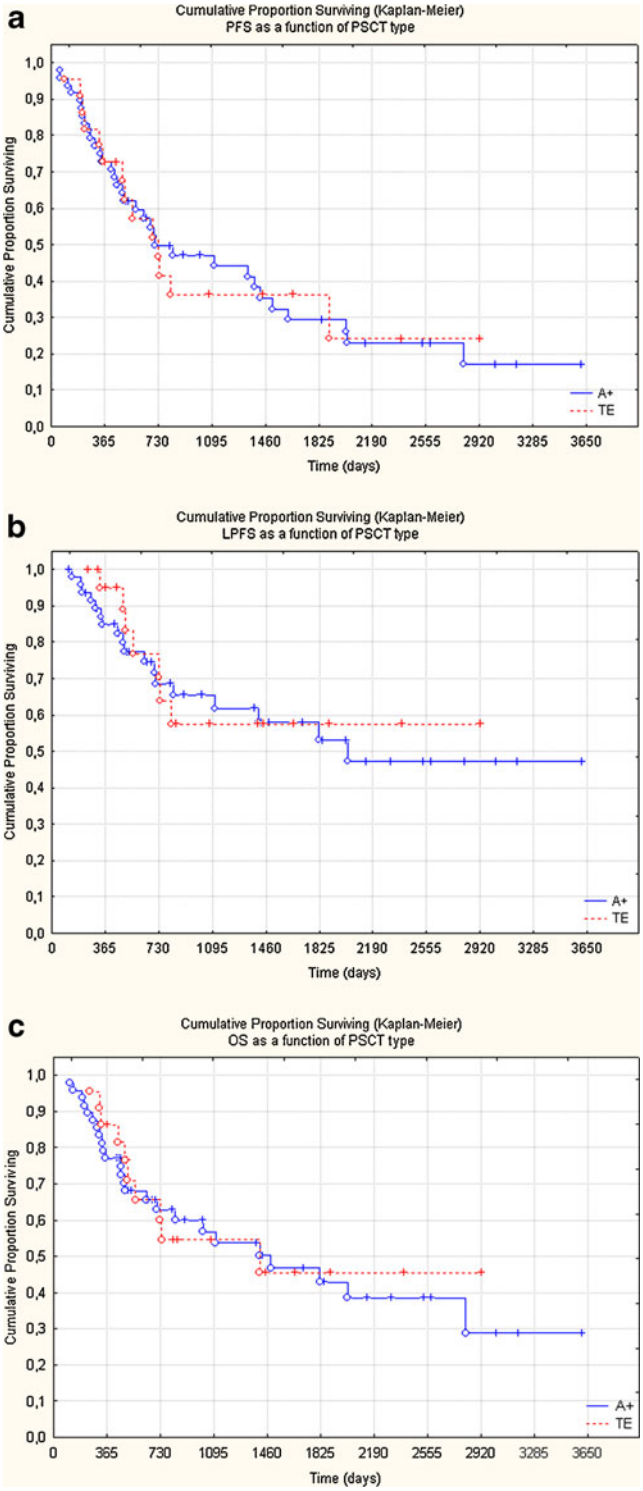

Fig. 2 Type of PSCT and survival parameters. Kaplan-Meier survival curves. **a** PFS; **b** LPFS; **c** OS (N=70). Note: Comparing A+vs TE: PFS Z=-0.01 (p=0.99); LPFS Z=-0.53 (p=0.60); OS Z=-0.35 (p=0.73)

therapeutic decisions—i.e. *continue or change the initial protocol—based on the early response,* were evaluated in different trials. On the basis of developed nomograms pCR and metastasis-free survival is predictable; low and intermediate-high chemotherapy sensitive patients can be identified, helping to determine who will benefit the most from an optimized schedule of paclitaxel after four course of antracycline [22]. Authors of this study suggest to those who have low probability to achieve pCR after anthracycline treatment should be steered toward clinical trials incorporating novel agents that may revert that kind of chemotherapy resistance. Aberdeen trial [30] patients with clinical responses were randomly assigned to continue the previous doxorubicin-containing regimen, or T and others with no responses were continued on T. That practice increased the rate of clinical responses and pCRs in the responding group, but just marginally improved the outcome in the non-responders. With opposing results, GeparTrio investigators [13] randomized patients not responding to initial TAC protocol to a non-cross-resistant (vinorelbine-capecitabine; NX) protocol or to continue TAC, and showed that the efficacy of NX was not inferior to TAC. In residual disease after PSCT, usage a non-cross resistant adjuvant protocol different from preoperatively used regimens has not demonstrated significant DFS advantage, but there was a trend favoring the use of non-cross resistant protocol [40]. However, we cannot draw firm conclusions from these trials, since they were little or not at all concerned of IBC patients. Dividing the perioperative chemotherapy into pre- and postoperative parts also seems to improve the survival parameters in our group of patients, as that setup has slightly improved the relapse-free survival on non IBC population [32], but it was not demonstrated in IBC series so far. In line with this in GeparTrio trial, splitting of protocol to a presurgical and adjuvant part seems significantly better than if it would be given as complete PSCT.

Conclusions

Achieving resecability leading to longer survival is the key point in the management of IBC, so the most effective protocols must be chosen. Definition of pCR has profound effect on further clinical decisions. Achieving (p)CR with a PSCT has prognostic value for a longer survival. In our selected IBC patient group, we did not detect any meaningful differences between A+and the concomitant TE protocols suggesting, that we should utilize third generation concomitant or sequential taxane-antracycline regimens with integrating novel targeted therapies. Six cycles of CT could be enough for patients achieving cCR, however for patients not achieving cCR after 3–4 cycles

PSCT, following decision making on changing the original PSCT to a non-cross-resistant chemotherapy could serve better the patient's interest, than using a fixed 6 cycles of chemotherapy.

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