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ORIGINAL ARTICLE

Clinical and pathological response to induction chemotherapy used as a prognostic factor in inflammatory breast cancer. Single institution experience

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Summary

Purpose: *To evaluate clinical and pathological characteristics of patients with inflammatory breast carcinoma (IBC). Also, to evaluate the importance of achieved clinical and pathological responses to induction chemotherapy (iCT) and their role in the prognosis of IBC.*

Methods: *The medical records of 81 female patients with stage IIIB IBC, diagnosed between January 2008 and December 2010 at the Institute for Oncology and Radiology of Serbia (IORS) were evaluated. Almost all of the patients received anthracycline-based iCT. After 3-4 cycles of iCT, the clinical response (defined as complete response/CR, partial response/PR, stable disease/SD and disease progression/PD) was assessed. Also, pathological response to iCT (defined as pathological complete response/pCR, near complete response/pNCR, partial response/pPR and no change/pNC) was estimated in patients who had undergone surgery. All first metastatic sites were recorded.*

Results: *Clinical CR/PR was observed in 61.8% of the patients, while the pathological response (pCR, pNCR/near complete response, and pPR) rate in patients who had undergone surgery was 70%. During follow-up 22 (27.2%) patients developed PD (8 responders and 14 non-responders). Most common metastatic sites were the skeleton in non-responders and the liver in responders. Central nervous system (CNS) metastases developed in 24% of non-responders while no responder developed such metastases. Non-responders had shorter OS compared to responders, but without statistical significance.*

Conclusion: *Although the number of the patients analysed in this study is relatively small, we believe that response to iCT could be used as a prognostic marker, since patients who initially failed to respond to iCT showed a higher risk for PD with development of distant metastases, primarily in bones and CNS, and shorter survival.*

Key words: induction chemotherapy, inflammatory breast cancer, pathologic complete response, prognostic factor, response rate

Introduction

IBC is a rare but the most lethal form of primary breast cancer (BC), accounting for 1-5% of all BC cases. Its prognosis is very poor, with a 3-year survival rate of only about 40%, compared with 85% in non-IBC patients, and 5-year survival rate is less than 15% [1-3]. At initial diagnosis metastases are present in up to 30% of the patients and patients are usually younger than patients with non-IBC [1,2,4].

As a specific form of breast carcinoma, IBC was first recognised by Lee and Tannenbaum in 1924, and the criteria of diagnosis had not been changed ever since [5]. The minimum criteria required for the diagnosis of IBC are rapid onset of breast erythema occupying at least one-third of the breast, with typical oedema (peau d'orange) and/or warm breast, with or without underlying palpable mass and pathological confirmation of invasive carcinoma from a core biopsy of the breast [6]. The most characteristic pathological finding of IBC on biopsy is invasion of the dermal lymphatics (IDL) by tumor emboli that impede the flow of lymph fluid, mimicking inflammation that is actually caused by tumor emboli [7]. Confirmation of IDL is no longer considered as compulsory criterion for diagnosis.

IBC is more often diagnosed in younger patients [2,4,8], with higher percentage of HER2 overexpression [9-11] and higher percentage of negative hormone receptors, in comparison with other BC types [9,12-14].

However, these combined clinical and pathologi-

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cal criteria can often be confused with locally advanced BC (LABC), which could be a limiting factor in comparing results of different studies that have examined the prognostic outcomes of women with IBC [15].

Treatment has not been precisely defined, and IBC is treated with iCT as LABC, with or without radiotherapy, and with or without surgery, depending on the response to iCT. Overall prognosis is usually poor, with low 5-year survival, but in recent years, more favorable prognosis has been reported in some studies, where IBC patients were treated in a multidisciplinary fashion [16].

The aim of this study was to evaluate the incidence of IBC at IORS, characteristics of patients and IBC, treatment options as well as treatment outcome, with special focus on pathological evaluation of response to iCT.

To the best of our knowledge, this is the first report regarding IBC in Serbia.

Methods

IORS is the biggest oncology institution in Serbia, covering more than 4 million people. Each year, more than 1500 new BCs of various stages are being diagnosed. We have evaluated all BC data charts to identify patients with IBC covering a 3-year period.

From January 2008 to December 2010, 98 female patients have been diagnosed with IBC. Only patients with stage IIIB disease were included in this analysis and 81 medical records were available for evaluation. The diagnosis of IBC was clinical, based on typical clinical signs of cancerous mastitis i.e. skin changes in the form of peau d'orange with diffuse erythema. All patients had histologically proven BC, with or without IDL. Estrogen and progesterone receptors (ER, PgR) were obtained from biopsy and assessed according to Allred score [17], while HER2 status was assessed by immunohistochemistry (IHC) (HercepTest, Dako). Mammography was performed initially in all patients and the main diagnostic criteria were skin thickening, with or without underlying breast tumor. All patients had complete initial evaluation, including chest and bones radiography, and ultrasound or computerized tomography of the abdomen. Treatment decision was always considered by the multidisciplinary tumor board and the first therapeutic choice was iCT (anthracycline-based/FAC or FEC) in the majority of patients if no contraindication existed, with or without radiotherapy. Treatment results were evaluated after the first 3-4 cycles, clinically and by mammography, based on the decrease in tumor and node size and skin changes, and were classified as follows: CR - complete disappearance of previously palpable breast tumor, no clinical and mammographic signs of cancerous mastitis and no enlarged regional lymph nodes; PR - response >25%; SD - response ≤25% with no new lesions; and PD - progression or appearance of new lesions.

Depending of the registered response, treatment was continued, changed to second line chemotherapy or complemented with radiotherapy. Selected patients with CR or PR were subjected to surgery. In patients who underwent modified radical mastectomy to remove the remaining tumor and nodes, the pathological response was evaluated and classified as: class I - pCR (no evidence of residual tumor in the breast or axillary lymph nodes), class II - pNCR (presence of *in situ* carcinoma in the breast, no invasive tumor, and no tumor found in the lymph nodes), class III - pPR (presence of residual tumor evidently modified by treatment) and class IV - pNC (histologically unmodified tumor), according to Chevallier et al. [18].

After surgery and/or radiotherapy, treatment decision was made individually for each patient according to the response to iCT and hormone receptor status of the tumor. All patients with hormone receptor-positive IBC received hormonal therapy at some point of their treatment. Also, patients with HER2-positive tumors received trastuzumab.

Time to progression (TTP) for patients who responded to iCT, including CR, PR and SD, was calculated from date of diagnosis to the date of relapse. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or last follow-up visit.

Statistical analysis

Microsoft Office Excel was used to prepare all graphics. For data processing the statistical package R [version 2.8.1 (2008-12-22); Copyright (C) 2008. The R Foundation for Statistical Computing; ISBN 3-900051-07-0] was used. The methods of descriptive statistics used were: frequencies, percentages and measures of central trend (mean and median values) and measures of variability (standard deviation/SD, and range). For testing the differences between parameters the Fisher's exact test and Pearson's x^2 test were used. Curves of probabilities for OS and TTP were constructed using the Kaplan-Meier product-limit method.

A p-value of <0.05 was considered as statistically significant.

Results

Patient characteristics

The median age at diagnosis was 56.3 years (range 28-77) and 26% of the patients were premenopausal. Five patients (6.1%) were younger than 40 years, with median age 32 years (range 28-38). Two patients had previous history of malignancy, one with contralateral BC (6 years earlier) and one with lung cancer. Positive family history for BC was found in 6/81 (7.4%) patients, one (1.2%) had ovarian cancer in family and 19 (23.5%) patients reported presence of other cancer types in close relatives (Table 1).

All tumors were staged as T4d and 59.3% had N2 nodal stage.

Histological analysis confirmed ductal carcinoma in 50.6%, IDL in 45.7% and 13.6% of the patients had only IDL without underlying tumor. Estrogen receptors (ER score ≥4) were positive in 40.7%. HER2 overexpression was found in 49.4% of the patients (Table 2).

Treatment modalities

All except 2 patients received anthracycline-based iCT. If no response was detected, taxanes-based second line chemotherapy was used. Preoperative radiotherapy was given to 36/81 (44.4%) patients.

Postoperatively, adjuvant chemotherapy was ad-

Table 1. Patient characteristics in 81 patients

Characteristics	*N (%)*
Age (years)	
Median 56	
Range 28-77	
≤40	6 (7.4)
>40	75 (92.6)
Menstrual status	
Pre-menopausal	23 (28.3)
Post-menopausal	58 (71.7)
Clinical node stage	
N0	5 (6.2)
N1	20 (25.0)
N2	48 (59.3)
N3	9 (9.5)
Previous malignancy	
Breast cancer	1 (1.2)
Lung cancer	1 (1.2)
No previous cancer	79 (97.6)
Positive family history	
Breast cancer	6 (7.4)
Ovary	1 (1.2)
Other	19 (23.5)
No malignancy in family	55 (67.9)

Table 2. Tumor characteristics in 81 patients

Tumor characteristics	*N (%)*
Histology	
Invasive ductal	41 (50.6)
Invasive lobular	13 (16.0)
Other	27 (33.4)
Tumor grade	
2	40 (49.4)
3	13 (16.0)
Unknown	28 (34.6)
Dermal lymphatics invasion	
Present	37 (45.7)
Absent	44 (54.3)
Estrogen receptors score	
<4	46 (56.8)
≥4	33 (40.7)
NA	2 (2.5)
Progesterone receptors score	
<4	53 (65.4)
≥4	26 (32.1)
NA	2 (2.5)
HER2	
Positive (IHC 3+ / CISH+)	40 (49.4)
Negative (IHC 0.1+ /CISH–)	38 (46.9)
NA	3 (3.7)

NA: not available

ministered to 32/43 (74.4%) patients, 21/43 (48.8%) received postoperative radiotherapy and 23/43 (53.5%) started hormonal therapy (mainly tamoxifen). Trastuzumab was administered to 33/40 (82.5%) HER2 positive patients; in 21/40 (52.5%) as neoadjuvant and in 12/40 (30%) as adjuvant therapy. Seven out of 40 patients (17.5%) with HER2 overexpression did not commence trastuzumab during the follow up period (Table 3).

Clinical response

Evaluation after 3-4 cycles of iCT showed CR or PR of tumor and axillary lymph nodes in 50/81 (61.8%) patients, 10/81 (12.3%) patients had SD, while PD was detected in 21/81 (25.9%) patients. Upon regression of IBC achieved with iCT (median 6.2 cycles, range 3-13) 43/81 (53%) patients underwent radical mastectomy. Among them, 13/43 (30.2%) patients also had preoperative radiotherapy.

Pathological response

Forty-three patients underwent radical mastectomy with axillary lymph node dissection. Tumor and nodal histological results were available in all patients. Results of pathological response to iCT were available for 30/43 (69.77%) breast specimens. pCR was confirmed in 6/30 (20%) patients, pNCR and pPR in 7/30 (23.3%) and 8/30 patients (26.7%), respectively. Overall response rate to iCT was 70% (Table 4).

Table 3. Treatment modalities in 81 patients

Treatment modalities	*N (%)*
Induction CT	
Anthracycline based±taxane	79 (97.6)
CMF	1 (1.2)
Docetaxel	1 (1.2)
Radiotherapy	
Preoperative irradiation	36 (44.5)
Postoperative irradiation	21 (25.9)
No radiotherapy	24 (29.6)
Operative treatment	
With preoperative RT	13 (16.1)
Without preoperative RT	30 (37.0)
No operative treatment	38 (46.9)
Adjuvant postoperative CT	
Administered	32 (39.5)
Not administered	11 (13.6)
No surgery	38 (46.9)
Endocrine treatment	
Tamoxifen	27 (33.4)
Aromatase inhibitors	2 (2.4)
No endocrine treatment	52 (64.2)
Trastuzumab	
Concurrent (pre op)	21 (25.9)
Sequential (post op)	12 (14.8)
No trastuzumab	48 (59.3)

RT: radiotherapy, CT: chemotherapy

Table 4. Pathological response to induction chemotherapy

Pathological response	*N (%)*
Complete	6 (20.0)
Near-complete	7 (23.3)
Partial	8 (26.7)
No change	9 (30.0)
Total	30 (100)

The median number of lymph nodes dissected was 15 (range 7-35) with median number of involved nodes 5 (range 1-29). Twenty-seven out of 43 operated patients (62.7%) had pathological confirmation of micrometastases in the evaluated axillary nodes.

TTP and OS

The patients' follow up ranged between 4-42 months (median 23). During that period, median TTP and OS were not reached. Kaplan-Meier curves for OS and TTP are shown in Figure 1. Six out of 81 (7%) patients died, including 2 patients with good initial response to iCT and 4 patients who failed to respond to iCT (Fisher's exact test; p=0.03).

Metastatic sites

A total of 22/81 (27.2%) patients had documented progression. Eight out of twenty-two (36.3%) patients were responders (CR, PR and SD) and underwent surgery, and 14/22 (63.7%) were non-responders, who failed to respond to iCT (Pearson x^2 test; $x^2_1=22.365$; $p= 2.25\times10^{-6}$).

All first metastatic sites were recorded and are shown in Table 5. The most common were bone metastases, registered in 5/14 non-responders and 3/8 responders (Fisher's exact test; p=0.35). Local recurrence was seen equally, in 3 patients in each group. Liver metastases were found in 3/8 vs. 2/14, and CNS in 2/8 vs. 3/14 responders and non-responders, respectively. Pleural metastases were confirmed in 3 patients and tumor in the contralateral breast in 2 patients - all non-responders. No lung metastases were found in both groups.

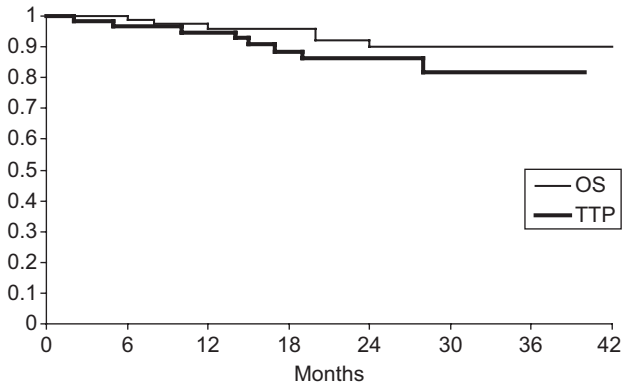

Figure 1. Kaplan-Meier estimate of overall survival and time to progression.

Table 5. First metastatic sites in patients with progressive disease

Metastatic site	*Responders*	*Non-responders*	*Fisher's exact test p-value*
	N (%)	*N (%)*	
Bones	3 (11)	5 (35)	0.35
Local recurrence	3 (33)	3 (18)	0.27
Liver	3 (33)	2 (18)	0.19
CNS	2 (0)	3 (24)	0.39
Contralateral breast	0 (0)	2 (12)	0.39
Pleura	0 (0)	3 (18)	0.24
Lung	0 (0)	0 (0)	1.00
Total	8 (100)	14 (100)	–

CNS: central nervous system

No statistically significant difference was observed in the frequency of the metastatic sites between these two groups of patients (Table 5).

Discussion

Despite multimodality treatment, IBC still has a worse prognosis than other stage IIIB BC forms, with statistically significantly lower OS rate (p=0.0001) [19]. Five-year OS is less than 15% [1] and 3-year OS is only about 40%, compared to 85% among patients with non-IBC [2,3].

The current consensus treatment for women with IBC is iCT with an anthracycline-based regimen, possibly combined with a taxane [3, 20-26]. Chemotherapy alone gives an overall response rate (ORR) of 65-76% and in combination with surgery and/or radiotherapy the ORR increases to 80% [20,21,25]. A trial performed at the M.D. Anderson Cancer Center in 2001, however, showed that addition of paclitaxel improves tumor resectability when used in anthracycline-refractory IBC [25]. pCR achieved after anthracycline-based regimens has been reported to range between 3-10% [27]. Addition of paclitaxel increases the pathological response rate to 19-25% [27,28]. The administration of trastuzumab is recommended to women with HER2-positive IBC. Recent trials showed that addition of trastuzumab in the neoadjuvant setting is being associated with higher pCR rates (38 vs. 19%) [29-32].

To date, the best prognostic indicator in IBC is response to iCT, both clinical and pathological, particularly if CR/pCR is confirmed [33-36]. IBC patients who respond to neoadjuvant chemotherapy are candidates for

mastectomy and axillary lymph node dissection [24,36]. At this stage, lymph node involvement has prognostic value as well, similar to any other BC type [35,37].

In our study we evaluated 81 stage IIIB IBC patients registered at IORS during a 3-year period. We observed good clinical response in 75% of them, while iCT completely cleared the breast of any microscopic evidence of invasive tumor in 20%, with pathological ORR observed in 70% of the analysed specimens. We showed that patients who initially failed to respond to iCT had a higher risk to develop distant metastases, primarily in bones and the CNS, and shorter survival. Unfortunately, due to the small sample size, we did not find any statistically significant difference for any first metastatic site comparing responders and non-responders, but we showed emphatically the important clinical significance of these findings.

Although the number of patients analysed in this article is relatively small and follow-up is rather short, we are convinced that this analysis can enrich the knowledge about IBC treatment and, at least, its short-term outcome. However, further research on IBC is required in order to further clarify the etiology and biology of this aggressive entity.

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