JBUON 2018; 23(5): 1273-1280
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

The influence of breast cancer subtypes on the response to anthracycline neoadjuvant chemotherapy in locally advanced breast cancer patients

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Summary

Purpose: *The objective of neoadjuvant chemotherapy (NACT) for locally advanced breast cancer (LABC) is downstaging to achieve resectability. According to the protocol for the treatment of LABC more than 10 years ago, the routine NACT for LABC in Serbia consisted of 4 cycles of FAC (fluorouracil, doxorubicin, cyclophosphamide). The aim of this analysis was to assess the influence of biologic subtypes of BC on the response to NACT and on the disease outcome in these patients.*

Methods: *We analyzed 190 patients with median age of 52 years (range 26–74), diagnosed with LABC between Jun/2002 and Dec/2005 and treated with 4 cycles of FAC. Patients with clinical response to NACT (162/192;85.26%) were subjected to radical mastectomy after which the majority of them received 3 cycles of adjuvant FAC, adjuvant tamoxifen if HR-positive disease, and postoperative radiotherapy. We retrospectively determined by immunohistochemistry estrogen receptor (ER)/ progesterone receptor (PgR)/HER2 status from BC biopsies in all patients who were divided in 4 subgroups. Pathological complete remission (pCR) was defined as ypT0N0. The main end points were disease-free survival (DFS) and overall survival (OS). Statistics included Fisher's exact test, KaplanMeier product-limit method and Log-rank test.*

Results: *After a median follow up of 76 months (range 3–128) 104/190 patients (54.74%) experienced disease relapse, while 78/190 (41.05%) died. Of 157 patients with known receptor status the numbers of 4 subtypes were as follows: 31/190 (16.32%) triple negative (TN) BC, 22/190 (11.58%) HR–/HER2+, 97/190 (51%) HR+/HER2– and 17/190 (8.95%) HR+/HER2+. Ten out of 190 patients (6.17%) achieved pCR and had significantly longer DFS (Log-rank test, p=0.042), and a trend to prolonged OS (Log-rank test, p=0.092). There was a significant difference (Fisher exact test, $p=7.7\times10^{-6}$) between pCR rates among 4 BC subtypes: 3/31 (9.68%) in TNBC, 6/22 (27.27%) in HR–/HER2+, 0/97 in HR+/HER2– and 1/17 (5.88%) in HR+/HER2+ patients. This difference was achieved on the account of the difference between TNBC and HR–/HER2+ BC subtypes (Fisher's exact test, $p=6.85\times10^{-6}$, Bonferroni correction: 0.05/6=0.0083). There were no differences in DFS and OS between the 4 BC subtypes.*

Conclusion: *Although there was a significantly higher number of patients achieving pCR among HR–/HER2+ subtype compared to other BC subtypes, this did not translate into improvement in long-term disease outcome of these patients.*

Key words: *anthracycline NACT, LABC, response according to BC subtypes*

Introduction

LABC refers to an inoperable non-metastatic BC. It is a heterogeneous clinical entity defined as a tumor greater than 5 cm, or infiltration of the skin or chest wall. LABC also includes inflammatory breast cancers, as well as fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular,

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Received: 04/05/2018; Accepted: 30/05/2018

or internal mammary nodal involvement. Recent guidelines describe LABC as American Joint Committee on Cancer (AJCC) stage IIB in addition to stage III [1,2]. The management of LABC had evolved over the years and includes multidisciplinary approach with NACT, surgery, adjuvant systemic therapy, and radiotherapy (RT). The primary objective of NACT is to achieve resectability (downstaging) in inoperable LABC, or to facilitate tumor shrinkage and increase breast-conserving surgery rates in patients with large operable breast tumors (downsizing) [3]. Thus, NACT is the modality of choice in upfront treatment for the vast majority of LABC pts [4-6].

The efficacy of LABC treatment depends on some prognostic factors. Researchers had indicated that clinical prognostic factors such as clinical stage (involvement of regional lymph nodes, tumor size) and other prognostic factors (histological tumor type, proliferative index) had a significant influence on the risk of distant disease recurrence and patient survival [7]. Although there were many studies investigating the prognostic value of ER, PgR and human epidermal growth factor receptor type 2 (HER2) [8-11], tumor biomarkers expression studies are still warranted to explore the predictive value of BC subtypes defined by the combination of the above biomarkers for the response to NACT.

Methods

Patient selection

All patients included in the study (n=190) presented with LABC (stage IIB/III) between Jan/2003 and June/2006. The diagnosis of LABC was established clinically by physical and radiological examinations, followed by histopathological confirmation of the diagnosis obtained by biopsy of primary tumor, skin, or ipsilateral lymph node biopsy.

Patients were included in a single-institution, nonrandomized cohort study at the Institute for Oncology and Radiology of Serbia.

Patients

LABC patients were assessed for response to NACT using clinical and radiological techniques. This was correlated with pathological response, as well as with DFS and OS as long-term efficacy endpoints. DFS was defined as the time from radical breast surgery to loco-regional recurrence and/or distant disease relapse and/or contralateral breast cancer and/or primary tumor of other organ and/or death without disease relapse, while OS was defined as the time from diagnosis to death from any cause. The results were analyzed in the whole patient population as well as in 4 breast cancer subtypes defined by ER/PgR/HER2 status from biopsies, retrospectively determined using immunohistochemical stains in most patients. Patients were planned to receive 4 cycles of FAC regimen: fluorouracil 500 mg/m^2 i.v. D1 / doxorubicin 50 mg/m^2 i.v. D1 / cyclophosphamide 500 mg i.v. D1, every 3 weeks. Patients with clinical response to NACT were subjected to radical mastectomy after which the majority of them received up to 4 cycles (median 3 cycles) of adjuvant FAC chemotherapy, adjuvant tamoxifen if HR-positive disease, and postoperative RT. Clinical response was assessed according to the RECIST criteria [12] and categorized as clinical complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition to physical examination, an imaging confirmation of the breast tumor size was obtained in each patient before starting the first cycle of NACT, and again before surgery. Pathological CR was defined as total pathological complete response (tpCR), absence of invasive cancer and *in situ* cancer in the breast and axillary lymph nodes (ypT0 N0).

Immunohistochemistry

The expression levels of ER, PgR and HER2 were determined by immunohistochemical staining of formalin-fixed paraffin-embedded tumor tissue sections. Antibodies used for immunohistochemical staining were: anti-human ERα (clone SP1, 1:200 dilution; LabVision), anti-human PR (clone PgR 636, 1:500 dilution; Dako), and anti-human HER2 (clone CB11, 1:800 dilution; Novocastra). Cut-off values for positive hormone receptors' (HR) status (Allred score) for both ER and PR were 3-8 [13]. Negative HER2 status was defined as IHC 0 and IHC1 + and IHC 2+/CISH (chromogenic *in situ* hybridization) - negative tumors [14].

Statistics

Descriptive statistical methods (frequencies, percents, mean, median, standard deviation [SD], and range) were used to summarize the data. The statistical significance level was set at p=0.05 and the Bonferroni correction was used for multiple testing at the same set of data. For data testing, the Fisher exact test was used. Curves of probabilities for time to DFS and OS were constructed using the Kaplan-Meier product-limit method; the median of survival analysis with corresponding 95% CI were used for description, and the Log-rank test was used for testing differences between curves for time to DFS and OS. The statistical analysis was done with the program R (version 3.3.2 (2016-10-31) - "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit); downloaded: January 21, 2017).

Results

Patients, disease and therapy characteristics, and disease relapse and outcome

The majority of 190 female patients were postmenopausal (61.05%), diagnosed with stage III disease [98/190 (51.58%) with IIIA and 84/190 (44.21%) with IIIB stage], and had grade 1+2 ductal and lobular invasive breast cancers. HR-positive

Table 1. Patients, disease and therapy characteristics, and disease outcome

Characteristics	*n (%)*	*Characteristics*	*n (%)*
Age (years)		Clinical response rates	
Mean (SD)	51.92 (8.34)	RR (CR+PR)	124 (65.26)
Median (Range)	52 (26-74)	non-RR (SD+PD)	66 (34.74)
Menopausal status		Mammographic response	
Premenopausal	74 (38.95)	CR	9 (4.74)
Postmenopausal	116 (61.05)	PR	73 (38.42)
Clinical stage		SD	78 (41.05)
IIB	4 (2.11)	PD	10 (5.26)
IIIA	98 (51.58)	No data	20 (10.53)
IIIB	84 (44.21)	Mammographic response rates	
IIIC	4 (2.11)	RR (CR+PR)	82 (43.16)
Tumor pathology (biopsy)		Non-RR (SD+PD)	88 (46.32)
IDC	81 (42.63)	No data	20 (10.53)
ILC	53 (27.89)		
Invasive Ca	44 (23.16)	Breast surgery	
Others	12 (6.32)	Radical	162 (85.26)
Tumor grade (biopsy)		Palliative	9 (4.74)
Grade 1+2	152 (80)	Without	19 (10)
Grade 3	14 (7.37)	Tumor pathology (surgery)	
No data	24 (12.63)	Ductal invasive	101 (53.16)
Estrogen receptor (ER)		Lobular invasive	70 (36.84)
ER-	76 (40)	Other	19 (10)
ER+	114 (60)	Total pathological response	
Progesterone receptor (PgR)		Non-CR	160 (84.21)
PgR-	100 (52.63)	CR	10 (5.26)
PgR+	90 (47.37)	No data	20 (10.53)
Hormone receptors (HR)			
HR- (ER- and PgR-)	66 (34.74)	Adjuvant FAC	
HR+ (ER+ and/or PgR+)	124 (65.26)	Without	55 (28.95)
HER2 status		With	130 (68.42)
HER2-	128 (67.37)	No data	5 (2.63)
HER2+	39 (20.53)	Adjuvant TAM	
No data	23 (12.11)	Without	76 (40)
HR & HER2		With	108 (56.84)
HR-/HER2-	31 (16.32)	No data	6 (3.16)
HR-/HER2+	22 (11.58)	Type of RT	
HR+/HER2-	97 (51.05)	Without	65 (34.21)
HR+/HER2+	17 (8.95)	Postoperative RT	102 (53.68)
NACT		Preoperative RT	11 (5.79)
FAC	190 (100)	Palliative RT	7 (3.68)
Number of cycles		No data	5 (2.63)
Mean (SD)	3.96 (0.61)		
Median (Range)	4 (1-9)	Disease relapse	
Clinical response		Without	86 (45.26)
CR	3 (1.58)	With	104 (54.74)
PR	121 (63.68)	Patients' outcome	
SD	48 (25.26)	Dead	112 (58.95)
PD	18 (9.47)	Alive	78 (41.05)
Total patients	190 (100)	Total patients	190 (100)

DCI: invasive ductal carcinoma, ILC: invasive lobular carcinoma RR: response rate, non-RR: non-response rate, NACT: neoadjuvant chemotherapy, RT: radiotherapy, TAM: Tamoxifen

tumors (ER+ and/or PgR+) were found in 124 (65.26%) patients. All patients received a median 4 cycles (range 1-9) of FAC NACT.

Objective clinical response was achieved in 124/190 (65.26%) patients (CR in 1.58% and PR in 63.68%), while 82/190 (43.16%) patients had objective response assessed by mammography. Resectability was achieved in 162/190 (85.26%) patients; (Table 1), all having radical breast surgery performed. Most of the patients had invasive ductal BC (53%), while lobular and invasive cancers without definitive specification were less frequent (37% and 10% respectively; Table 1). Total pathological response (tpCR) was achieved in only 10/190 (5.26%) patients. Adjuvant FAC chemotherapy was administered to 130/190 (68.42%) patients, while 108/190 (56.84%) patients received adjuvant endocrine therapy. More than half patients had postoperative RT (53.68%; Table 1). Patients, disease and therapy characteristic are shown on Table 1.

After a median follow up period of 76 months (range 3-128), 104/190 (54.74%) patients experienced disease relapse, while 78/190 (41.05%) died. For operated patients, median DFS was 76 months (95% CI: ≥61 months), while median OS was not reached (Table 1; Figure 1).

DFS and OS according to response to NACT

Response rates and median (95%CI) DFS and OS according to response to NACT are shown on Table 2 and Figures 2, 3, 4, 5 and 6. Among 161 operated patients objective clinical response (CR + PR) was achieved in 121 of them (74.70%) who also had significantly increased DFS compared to patients with no objective clinical response (Log Rank test, p<0.01; Table 2, Figure 2). Ten out of 162 (6.26%) radically operated patients who achieved tpCR had significantly increased DFS compared to patients without pCR (Log Rank test, p<0.05; Table 2, Figure 3). Similarly, patients who achieved objective clinical response (124/190) had significantly increased OS compared to patients without objective response to NACT (Log Rank test, p<0.01; Table 2, Figure 4). Furthermore, 82/190 (48.24%) patients with objective mammographic response (CR+PR) had also significantly increased OS compared to patients with mammographically SD/PD (Log Rank test, p<0.01; Table 2, Figure 5). However, there was a trend toward increased OS in 10 out of 190 patients (5.26%) achieving pCR compared to patients with non-pCR (Table 2; Figure 6).

Table 2. Response rates and DFS/OS according to the response to NACT

DFS (months)	*n (%)**	*Median (95%CI)*	*Log-rank test*
Radically operated patients	162/190 (85.26)	76 (≥61)	-
Clinical response			p<0.01
CR+PR	121 (74.70)	99 (≥75)	
SD	41 (25.30)	36 (≥30)	
Mammographic response			ns
CR+PR	80 (54.45)	77 (≥63)	
SD	67 (45.55)	71 (≥37)	
Pathological response			p<0.05
non-pCR	152 (93.83)	73 (≥53)	
pCR	10 (6.17)	Not reached	
OS (months)	*n (%)*	*Median (95%CI)*	*Log-rank test*
Whole group	190 (100)	Not reached	-
Clinical response			p<0.01
CR+PR	124 (65.26)	Not reached	
SD+PD	66 (34.74)	47 (42-73)	
Mammographic response			p<0.01
CR+PR	82 (48.24)	Not reached	
SD+PD	88 (51.75)	78 (≥56)	
Pathological response			ns
non-pCR	160 (94.12)	Not reached	
pCR	10 (5.88)	Not reached	

*response rates; DFS only for radically operated patients; OS for all analyzed patients; ns: not statistically significant

Pathological response to NACT according to BC biologic subtypes

One hundred and fifty-seven patients with known HR and HER2 status were divided into 4 subgroups according to biologic subtypes: 1) triple negative (TN) BC subgroup: 31/190(16.32%), 2) non-luminal/HER2+ (HR-/HER2+) subgroup: 22/190 (11.58%), 3) luminal/HER2- (HR+/HER2-) subgroup: 97/190 (51%) and 4) luminal/HER2+ (HR+/HER2+) subgroup: 17/190 (8.95%) (Table 3).

There was a statistically significant difference in pCR rate among these 4 BC subtypes: 3/31

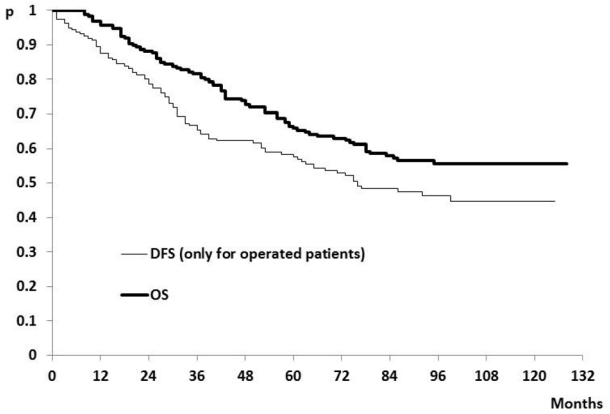

Figure 1. Overall survival (OS) and disease-free survival (DFS) in the whole group of patients.

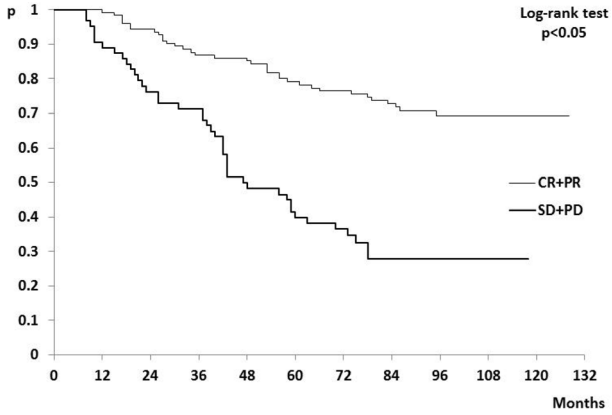

Figure 4. Overall survival according to clinical response (CR+PR vs SD+PD).

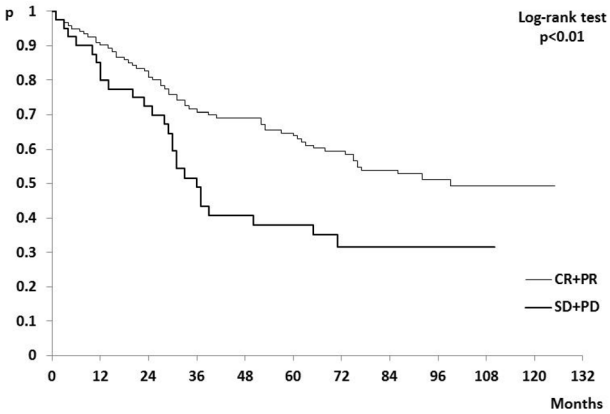

Figure 2. Disease-free survival according to clinical response (CR+PR vs SD+PD).

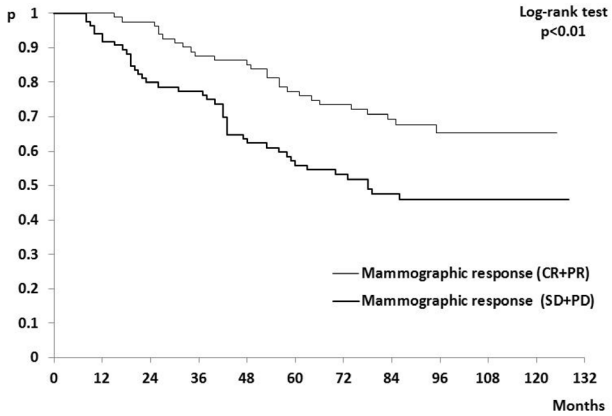

Figure 5. Overall survival according to mammographic response (CR+PR vs SD+PD).

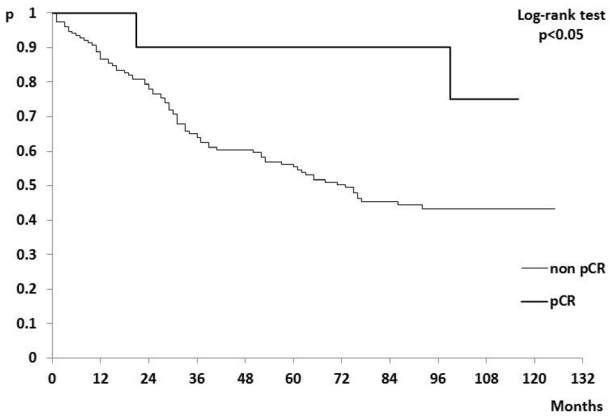

Figure 3. Disease-free survival according to pathological response (pCR vs non-pCR).

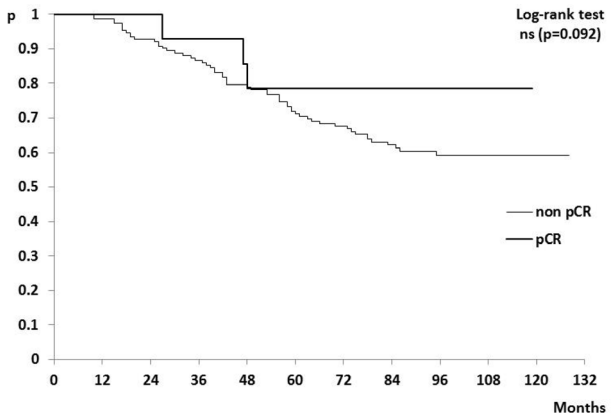

Figure 6. Overall survival according to complete pathological response (pCR vs non pCR).

Table 3. Clinical, mammographic and pathologic response rates according to 4 biologic BC subtypes

Response to NACT	*ER/PgR & HER2 categories*					*Fisher's exact test p*
	HR- / HER2- n (%)	*HR- / HER2+ n (%)*	*HR+ / HER2- n (%)*	*HR+ / HER2+ n (%)*	*No data*	
Clinical response rates						ns
CR+PR	15 (48.39)	14 (63.64)	64 (65.98)	14 (82.35)	17 (73.91)	
SD+PD	16 (51.61)	8 (36.36)	33 (34.02)	3 (17.65)	6 (26.09)	
Mammographic response rates						<0.05
CR+PR	7 (22.58)	12 (54.55)	41 (42.27)	11 (64.71)	11 (47.83)	
SD+PD	20 (64.52)	8 (36.36)	45 (46.39)	4 (23.53)	11 (47.83)	
No data	4 (12.9)	2 (9.09)	11 (11.34)	2 (11.76)	1 (4.35)	
Pathological response rates						<0.01
pCR	3 (9.68)	6 (27.27)	0 (0)	1 (5.88)	0 (0)	
non pCR	23 (74.19)	11 (50)	90 (92.78)	15 (88.24)	21 (91.3)	
No data	5 (16.13)	5 (22.73)	7 (7.22)	1 (5.88)	2 (8.7)	
Total	31 (100)	22 (100)	97 (100)	17 (100)	23 (100)	-

ns: not statistically significant

Table 4. Mammographic and total pathological response rates according to pairs of ER/PgR & HER2 categories

Groups	*Fisher's Exact test*
Mammographic response	
(HR-/HER2-) vs (HR-/HER2+)	p=0.03428
(HR-/HER2-) vs (HR+/HER2-)	p=0.07301
(HR-/HER2-) vs (HR+/HER2+)	p=0.0042
(HR-/HER2+) vs (HR+/HER2-)	p=0.4571
(HR-/HER2+) vs (HR+/HER2+)	p=0.48854
(HR+/HER2-) vs (HR+/HER2+)	p=0.09327
Total pathological response	
(HR-/HER2-) vs (HR-/HER2+)	p=0.12207
(HR-/HER2-) vs (HR+/HER2-)	p=0.01026
(HR-/HER2-) vs (HR+/HER2+)	p=1
(HR-/HER2+) vs (HR+/HER2-)	$p=6.85 \cdot 10^{-6}$
(HR-/HER2+) vs (HR+/HER2+)	p=0.08545
(HR+/HER2-) vs (HR+/HER2+)	p=0.15094

Bonferroni correction: 0.05/6=0.0083; bold numbers denote statistical significance

(9.68%) in TNBC, 6/22 (27.27%) in non-luminal/HER2+, 0/97 in luminal/HER2-, and 1/17 (5.88%) in luminal/HER2+ patients (Table 3). This difference was achieved on the account of the difference between non-luminal/HER2+ and luminal/HER2- BC subtypes (Fisher's Exact Test, $p= 6.85 \times 10^{-6}$, Bonferroni correction: 0.05/6= 0.0083, Table 4). There was no difference in DFS and OS between the 4 subgroups of patients with different BC biological subtypes.

Discussion

The rationale for NACT is based on its usefulness in quickly evaluating the efficacy of primary systemic chemotherapy through pCR as surrogate endpoint for long-term outcome [15]. Furthermore, neoadjuvant approach is offering opportunity to investigate the influence of different predictive markers on response [16-19].

The expression of tumor ER and PgR was identified as an independent variable that was significantly associated with the likelihood of achieving pCR. In a retrospective analysis of 1731 patients treated with various neoadjuvant regimens, pCR rates were 24% in patients with ER- tumors and 8% in patients with ER+ tumors (p< 0.001), regardless of treatment regimens applied [20]. Multiple large prospective neoadjuvant clinical trials also showed that pCR rates were significantly higher in patients with HR- tumors [21].

HER2 is overexpressed in 15-20% of BC patients and this is associated with poor survival [22]. However, it was demonstrated that HER2 overexpression was associated with an increased benefit from anthracycline-based regimens [23]. Furthermore, changes between ER/PgR/HER2 status in native tumor before and after NACT were also found to be of prognostic and predictive value [24,25].

Our study aimed to assess the influence of biologic BC subtypes defined by ER/PR/HER2 tumor expression on immediate response to NACT and, also, on the long-term disease outcome in these

patients. In our analyzed group only 6.17% patients achieved pCR, which is less than expected and could be explained by inferiority of the NACT regimen used. Clinical studies reported pCR rate of 10-13 if anthracycline-only containing regimens were applied in the neoadjuvant setting, as compared to 16-20% pCR with sequential use of antracycline-taxane regimens [26]. Our analysis also showed that patients achieving pCR had significantly longer DFS (Log-rank test, p=0.042) and trend to prolonged OS (Log-rank test, p=0.092) in comparison to patients without pCR, suggesting that no matter which chemotherapy regimen is used, achieving pCR is associated with favorable prognosis in LABC patients.

A lot of work has been done investigating the association of BC subtypes with pCR to NACT, and the impact on survival [27,28]. The key findings concerning the influence of HR/HER2 BC subtypes on disease outcome came from CTNeoBC pooled analysis [29]. At the individual level, the association between pCR and long-term outcome was strongest in the patients with TNBC (EFS: HR=0.24 with 95% CI: 0.18–0.33; OS: HR=0.16 with 95% CI: 0.11–0.25) and in those with non/luminal/HER2- tumors who received trastuzumab (EFS: HR=0.15 with 95% CI: 0.09–0.27; OS: HR=0.08 with 95% CI: 0.03-0.22) [26]. Our results found a statistically significant difference (Fisher's Exact test, $p=7.7\times10^{-6}$) in pCR rate among 4 BC subtypes, with the highest pCR in non-luminal/HER2+ BC patients. This difference was achieved on the account of the difference between non/luminal/HER2+ and luminal/HER2- BC subtypes. In our study, patients with TNBC achieved pCR of only 9.68%, a result which is not in line with newer literature data [30,31]. Although the small number of TNBC patients in our group compromises the interpretation of these results, low pCR rate noted in TNBC patients is in line with the recommendation that the combination of anthracycline and taxane chemotherapy is superior to anthracyclines alone [32].

Moreover, in our analysis we did not find differences in DFS and OS between the 4 biologic BC subtypes. These findings are different from the results of von Minckwitz et al. [33]. The authors reported that the achievement of pCR was associated with improved DFS in luminal B/HER2- (p=0.005), non-luminal/HER2+ (p<0.001), and TNBC (p<0.001) but not in luminal A (p=0.39) or luminal/HER2+ (p=0.45) BCs. Achieving pCR in non-luminal/HER2+ and TNBCs was associated with excellent prognosis. The explanation for the difference between our and von Minckwitz [33] results might be the small number of analyzed patients and, accordingly, the small number of events, as well as inferiority of the NACT regimen we used [34]. To further improve the outcome of BC patients receiving NACT, oncologists in Serbia created a Serbian consensus of NACT for BC [35].

Conclusions

Although there was a significantly higher number of patients achieving pCR among HR–/HER2+ subtype compared to other BC subtypes, this did not translate into improvement in long-term disease outcome of these patients.

Acknowledgements

We thank our colleague Dr. Ljiljana Vuckovic-Dekic for help and support in finalizing this manuscript.

Conflict of interests

The authors declare no conflict of interests.

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