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SPECIAL ARTICLE

Serbian consensus of neoadjuvant therapy for breast cancer: NeoPULSE

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Summary

Even though surgery is the primary treatment of operable breast cancer, it has been known for decades that the administration of postoperative adjuvant or preoperative neoadjuvant therapy is extremely important. Indications for neodjuvant therapy administration have been expanded over the years, and nowadays this kind of treatment represents an inevitable option in early breast cancer treatment. The NeoPULSE project, which gathered a group of experts in the field of breast cancer from five Serbian university centres, was formed with the aim to define optimal breast cancer diagnosis, indications for neoadjuvant therapy, therapeutic combinations in relation to molecular/biological parameters of breast cancer, as well as the treatment after neoadjuvant therapy.

During two separate expert meetings involving surgeons, medical oncologists, radiation oncologists, a pathologist, and a "Blueprint" workshop, the project participants answered questions over the indications for neoadjuvant therapy.

The first part covered local practice and referred to the existence and work of a multidisciplinary team, as well as commonly applied therapeutic regimens in the neoadjuvant setting. Experts analysed personal views regarding indications for the administration and benefits of neoadjuvant therapy, their perception on the correlation between achieving a pathological complete response (pCR) and the outcome of treatment, as well as the attitude towards controversies about this type of treatment, primarily regarding a possible change in the receptor status after therapy and therapeutic options after a suboptimal response.

The analysis of the answers pointed to problems and deviations from recommendations in everyday clinical practice, based on which appropriate solutions were proposed.

The establishment of such a panel and consensus is an attempt to modernize multidisciplinary teams in Serbia, achieve reaching uniform decisions of all subjects dealing with breast cancer, and therefore, at least in one segment, improve breast cancer treatment in Serbia.

Key words: *breast cancer, local practice, multidisciplinary team, neoadjuvant therapy, pathological complete response*

Introduction

Breast cancer is a complex disease, and its outcome mostly depends on its stage, biological characteristics and initial treatment, while treatment decision must be reached through a multidiscipli-

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nary team (MdT) with great experience in breast cancer treatment [1,2]. A MdT includes a surgeon, medical oncologist, radiologist, radiotherapist and a pathologist, all with experience in breast cancer diagnosis and treatment. Although surgery (with or without radiotherapy) has long been the primary treatment of operable breast cancer, it has also been known for a couple of decades that the administration of postoperative (adjuvant) or preoperative (neoadjuvant) chemotherapy (NAT) play extremely important roles. The main aim of chemotherapy in early and locally advanced breast cancer is to reduce the risk of distant metastases by targeting micrometastases [3,4]. Indications for the administration of NAT have expanded over the years. Initially, NAT was administered only to patients in whom surgery was not possible to ensure local control due to locally and/or regionally advanced breast cancer (LABC). In such patients, the administration of NAT is still practically the only initial therapeutic option, and the main aim is to achieve tumor resectability (downstaging), i.e. appropriate surgery with curative intent, which most often implied modified radical mastectomy [5-9]. Another important aim of NAT in LABC patients is tumor downsizing, enabling breast-conserving surgery in patients in whom radical mastectomy would be indicated due to a locally advanced tumor. According to literature data, breast-conserving surgery was performed in a large percentage of patients (up to 72%) in whom radical mastectomy would have been indicated if NAT hadn't been administered [10]. The third aim of NAT is the possibility of timely assessment of tumor chemosensitivity, i.e. fast assessment of the effects of treatment. In case there are no effects, NAT can be modified, i.e. an inefficient therapeutic combination can be changed, meaning that the patient will be spared the side effects. The assessment of therapeutic effects implies frequent clinical and radiological check-ups during NAT, following set criteria, and according to the assessment of surgeons and chemotherapists for each patient individually [11]. Furthermore, a positive effect, especially if it led to pCR of a tumor both in the breast and axillary and regional lymph nodes, not only indicates high tumor sensitivity to the applied treatment, but also a better long-term treatment outcome [12,13]. Despite a rational assumption that NAT could have a positive effect on overall survival (OS), so far no published clinical studies have confirmed better survival compared to the same regimens administered postoperatively (adjuvant therapy) [14]. However, it is possible that the longer the follow-up, the clearer the effect of achieving a pCR would become in relation to the outcome of treatment, i.e. disease-free survival (DFS) and OS.

The outcome of treatment, apart from the initial stage, is greatly influenced by histological characteristics of breast cancer, including the grade of differentiation and histological type, as well as immunobiological characteristics, expression of steroid receptors, HER2 status and proliferative activity (Ki67). Some biological characteristics of breast cancer may indicate whether the tumor will be more or less chemosensitive. Therefore, lobular carcinoma, with high estrogen receptor (ER) and progesterone receptor (PR) expression, HER2 negative, with a low proliferative index (Ki67) (luminal A-like), are generally less chemosensitive [12,13]. On the other hand, particularly chemosensitive breast cancers include the so-called triple negative disease (ER negative, PR negative, HER2 negative; TNBC) and HER2 positive breast cancer [12,13]. Given the possibility of using targeted therapy with trastuzumab in HER2 positive breast cancer, the diagnosis and treatment of these patients requires special attention to avoid unnecessary delay of the most efficient therapeutic modalities.

The NeoPULSE project, which gathered a group of experts for breast cancer from five Serbian university centres, was established with the aim to define the optimal diagnostic approaches, indications for NAT, therapeutic combinations in relation to molecular/biological parameters of breast cancer, as well as the treatment after NAT. The expressed views represent the consensus of experts in the field of breast cancer in Serbia.

Methods

The NeoPULSE project consists of the analysis of opinions of breast cancer experts on the indications for the administration of NAT. Answers to questions on the indications for NAT were obtained during two separate expert meetings and a "Blueprint" workshop. Questions which were included in the questionnaire had been made in cooperation with the project participants, whereas the answers were used for identifying problems and deviations from recommendations in everyday clinical practice, based on which appropriate solutions were proposed.

The first stage of the NeoPULSE project involved a group of experts in the field of medical oncology from five university centres: Institute of Oncology and Radiology of Serbia, Clinical Centre Nis, Institute of Oncology of Vojvodina, CHC Bezanijska kosa and Clinical Centre Kragujevac. The participants discussed and answered questions related to the concept of NAT for breast cancer patients. The questions were divided into several parts.

The first part included local practice and referred to the existence and work of a MdT. Furthermore, it assessed the approximate percentage of patients referred to a MdT for reaching a decision on the administration of NAT, and most commonly applied therapeutic regimens in that approach.

Next, viewpoints of medical oncologists regarding indications for the administration and benefits of NAT were analysed, as well as their perception about the correlation between achieving a pCR and the treatment outcome.

Finally, it examined the perception of oncologists about the importance of the results of the NEOSPHERE study [15], as well as their attitude towards controversies regarding the administration of NAT, primarily those associated with a possible change in the receptor status after NAT and therapeutic options after a suboptimal response.

Furthermore, a group of experts in the field of breast cancer surgery, including a consultant pathologist, followed a similar concept, reviewed and discussed their views regarding NAT. Some of the questions were the same, whereas issues regarding surgical treatment, radiological and pathological diagnosis were discussed additionally.

Afterwards, a meeting was organized for medical oncologists and surgeons to discuss results from the previous two meetings and reach mutual conclusions, i.e. consensus for the administration of NAT in breast cancer.

This consensus resulted in clear recommendations for the administration of NAT in breast cancer ("Blueprint").

Results and recommendations for everyday clinical practice

Local practice

Most international guidelines for breast cancer emphasize the importance of the multidisciplinary approach in the treatment, the existence of "Breast Unit" and other types of multidisciplinary decision-making that could lead to optimal treatment of breast cancer patients [2,16]. Moreover, the National guideline for breast cancer diagnosis and treatment highlights the requirement to have a MdT [1]. In this segment, the project participants answered questions regarding the functioning of the MdT, involvement in decision-making in the preoperative approach and diagnosis, primarily surgical, and problems associated with that segment, which is important for reaching decisions about treatment.

The following question regarding the MdT was posed: "Does your institution have a fully functional MdT that could indicate NAT?". All experts in the field of medical oncology, as well as 90% of surgeons, replied affirmatively.

However, 78% of medical oncologists commented that they had been consulted about preoperative treatment decision in only 10-30% of the cases.

The interpretation of this response is in favour of the fact that, despite the existence of the MdT, a considerable number of patients is not referred to preoperative consultations, meaning that the decision on the primary treatment is usually reached by a surgeon from the regional centre, whereas the MdT is involved in the treatment decision only after surgical treatment.

Special attention was paid to this issue at a joint meeting of experts in the field of medical oncology and surgery.

The conclusion is that decisions on the treatment of breast cancer patients must not be decided outside of MdT

The proposed solutions for the identified problems from everyday clinical practice include: the education of surgeons and oncologists from secondary healthcare institutions about the importance of preoperative diagnostics and the results of NAT administration, as well as a mandatory referral of all breast cancer patients immediately upon diagnosis to preoperative consultations (diagnostic-therapeutic) in a tertiary healthcare institution, i.e. to a consulting body which includes tertiary healthcare doctors.

Special attention was paid to the issue of insuffitient availability of core-needle biopsies in secondary healthcare institutions which can be overcome by improving the cooperation between healthcare institutions of a secondary and tertiary level. This problem was also perceived by selected surgeons from reference institutions. The answer to the question "For how many of 10 patients with non-metastatic breast cancer did you have a complete pathological result with ER, PR, and HER2 receptors and a Ki67 finding?" was 4-6 in 80% of the participants, whereas 20% of them answered 1-3, which is below the agreed standard minimum of 70%.

According to the National guide, imaging-guided percutaneous procedures are entirely under the jurisdiction of radiologists. It is recommended that more than 90% of patients with invasive and over 85% of patients with non-invasive breast cancer should have a histological diagnosis, without surgery [1].

Insufficient number of radiologists trained for this procedure is recognized as a problem for the implementation of these methods in all secondary healthcare institutions.

According to current recommendations of the European Society for Medical Oncology (ESMO),

with which the group of experts is in complete agreement that no therapeutic procedure should be initiated before the results of a core-needle biopsy (CNB) are obtained [17].

It has been suggested that a biopsy of palpable lesions should be done by a surgeon (in agreement with a radiologist at the institutional level), whereas biopsies of nonpalpable lesions should be done by an ultrasound-guided core-needle biopsy (CNB).

Fine needle aspiration (FNA) is a recommended method for obtaining material for the cytological diagnosis of clinically enlarged axillary lymph nodes.

A period from the biopsy to the referral to the MdT should not be more than 14 days, therefore, if a secondary healthcare centre doesn't have an MdT, it is advised to refer patients to a consulting body in a tertiary institution prior to any therapeutic decisions [1,2,16,17].

The next segment examined the experts' views on tumor characteristics, primarily tumor size as an important factor in reaching a decision about possible NAT. Moreover, current local practice on a secondary and tertiary level was discussed.

The experts agreed that in the tertiary centres where they work, patients with tumors bigger than 3 cm are referred to consultations regarding NAT. One fifth of surgeons (22%) and 10% of medical oncologists opted for NAT, even for tumors smaller than 2 cm. However, when the question "Which patients from your region are most often referred to consultations about NAT?" was posed, two thirds of surgeons (67%) said they referred only patients with tumors larger than 5 cm. That just confirmed the assumption that most secondary healthcare institutions still considered tumor size a crucial factor for the referral of patients to NAT consultations.

The recommendations of the European Society for Medical Oncology (ESMO) [17] highlight tumor size of 2 cm as a borderline which represents the indication for the use of NAT if breast-conserving surgery is not possible, i.e. even though the size itself is not always the main determinant for the use of such an approach, the MdT should consider the administration of NAT for tumors of that size for each patient individually.

Therefore, the authors of this paperwork want to particularly emphasize the fact that every physician involved in the treatment of breast cancer should refer the patient to a mandatory diagnostic biopsy, and then to preoperative consultations with the MdT for a decision on the treatment.

The experts mostly agreed on the indications for the administration of NAT: most surgeons (70%) and medical oncologists (90%) believed that the clinical/radiological involvement of lymph nodes, skin involvement (surgeons 80% and medical oncologists 90%), and chest involvement (surgeons 60% and medical oncologists 70%) are reasons for considering NAT. The initial stage of disease as a factor for administration of NAT was perceived differently, depending on the specialty of the participants. All medical oncologists, compared to 70% of surgeons, considered the stage of disease a significant factor in the assessment of the need for NAT administration.

Most surgeons (70%) believed that the possibility of breast-conserving surgery was a strong reason for the administration of NAT, whereas only 44% of medical oncologists shared that opinion.

Both medical oncologists and surgeons considered the molecular breast cancer subtype a significant factor which affected the decision on the administration of NAT.

The mutual viewpoint of the authors is that (T2) HER2 positive breast cancer is the indication for the administration of NAT.

Opinions were divided regarding triple-negative breast cancer (TNBC) and luminal B subtype: most medical oncologists (80%) and half of surgeons believed that patients with TNBC were candidates for NAT.

In patients with luminal B subtype, 20% of medical oncologists and 50% of surgeons considered patients with luminal B subtype candidates for NAT, even though the cancer was operable.

Medical oncologists suggested that the decision on NAT in patients with luminal B subtype should be reached for each patient individually, primarily regarding the general condition of each patient (explained in more detail further in the paperwork).

Most medical oncologists and surgeons didn't consider the age of patients a limiting factor for the administration of NAT, whereas the majority would not recommend NAT in patients with ECOG PS≥3. The stage of disease (II,III), tumor biology, general condition and patient preferences are factors to be analysed for each patient individually when reaching a decision on the primary breast cancer treatment.

In patients diagnosed with stage III breast cancer, there was a complete agreement to start the treatment with NAT.

The fact that 50% of the project participants believed that the administration of NAT was also indicated in stage IIB patients is in favour of the preoperative histopathological and IHH diagnosis and multidisciplinary decision-making on the primary treatment.

The importance of NAT concept

NAT increases the possibility of optimal surgery both in operable tumors and in locally advanced breast cancers, and leads to downstaging in axillary lymph nodes in 30-50% of the patients, therefore affecting the range of therapeutic procedures in the armpit [5,10]. The largest meta-analysis published in 2001 did not indicate that NAT led to the prolongation of either DFS or OS in comparison to adjuvant chemotherapy [14]. Nevertheless, at the time of the publication no data on the importance and relation between molecular subtypes of breast cancer and achieving a therapeutic response, primarily pathological complete remission, were available. Data on tumor heterogeneity now clearly indicate that different molecular tumor subtypes react differently to the administered chemo- and biological therapy. Achieving a pCR is the strongest prognostic factor of survival after NAT. pCR rates range, depending on a molecular subtype of breast cancer from 5% in luminal A subtype, to up to 60% in the most aggressive forms of highly proliferative hormone receptor (HR) negative tumors [13,15,18-20]. However, it has been identified that a pCR doesn't have the same prognostic and predictive significance in all breast cancer subtypes.

The meta-analysis conducted by von Mickwitz et al. [13] analysed the prognostic value of a pCR in different breast cancer subtypes. The results of this meta-analysis underlined the fact that the achievement of a pCR was not associated with a prolonged survival in luminal A subtypes. Similar was the case with luminal B/HER2 positive subtype (triple positive subtype), whereas in luminal B/HER2 negative, HR-/HER2 + and HR-/HER2- subtypes, achieving a pCR was a clear predictor of a longer OS and DFS.

The problem about the interpretation of the significance of a pCR has to do with the variations of the definition of a pCR in clinical studies. The definition is different since there are two possible interpretations of a therapeutic response: in the first, the achievement of a pCR is defined based on the presence/absence of invasive carcinoma in the breast only; in the second one, a pCR is defined based on the presence/absence of invasive carcinoma both in the breast and axillary lymph nodes. The results of two large meta-analyses [12,13] have shown that classifications systems which include invasive carcinoma in the breast only have little relevance, since metastases in lymph nodes clearly influence further the course of the disease. Therefore, unless complete tumor eradication is done, an overall response can't be defined as a pCR.

The importance of ductal carcinoma *in situ* (DCIS), as a non-invasive carcinoma after NAT is also vague, since the authors of the two analyses reached different conclusions.

Von Mickwitz et al. [13] concluded that the presence of DCIS negatively affected the survival of patients and that pCR should be defined as the absence of an invasive carcinoma in the breast and axillary lymph nodes, as well as the absence of DCIS (ypT0 N0).

In contrast, the authors of the FDA working group (CTNeoBC) concluded that the presence of DCIS did not affect OS and DFS/EFS, and that the definition of pCR, which should be used in practice and in the interpretation of results of neoadjuvant clinical studies, implied only the absence of invasive carcinoma in the breast and axilla, regardless of the presence of non-invasive DCIS (ypt0/is N0) [12]. There isn't a standardised approach in pathological reporting when it comes to the response to NAT. All proposed classification systems make a difference between a complete response, partial response or a lack of response to NAT. In order to make proper assessment of the pathological response to NAT, it is necessary to have an insight into imaging findings and clinical presentation of a tumor prior to the onset of the treatment.

Based on previous experience, the authors of the paperwork consider that pCR should be defined as ypT0N0, i.e. without *in situ* component, that tumor biology is a key predictive factor of the response to NAT and that it is certainly considered one of the parameters in the decision on the primary treatment of early breast cancer.

Surgical treatment after NAT

There are some dilemmas regarding surgical treatment after NAT: possible breast-conserving surgery (BCS), particularly in multifocal and multicentric tumors, the axilla surgery instead of sentinel lymph node biopsy (SLNB) after NAT depending on the status of axillary lymph nodes prior to NAT.

The general conclusion of surgeons who participated in this project is that BCS is possible after NAT.

Special emphasis was put on the significance of adequate marking of the tumor site during core biopsy (for which a radiologist and a surgeon are in charge).

The marking is done by placing appropriate clips which enable tumor site visualisation. In case of a complete clinical and/or radiological response, the clips help a radiologist to do the marking/localization using a "harpoon" wire

(wire-guided localization), black carbon or a radiopharmaceutical (ROLL), which all enable a surgeon to remove a nonpalpable change [1].

Another important fact is the margin width after surgery, given that a positive margin is associated with local recurrence (0.6-1.5% a year). The main assumption for accurate estimation of the margin status is surgical orientation of the sample and correlation with mammography. There isn't a standardized method for the estimation of the margin status after quadrantectomy, nor a standardized number of samples to be checked for each of the bordering surfaces. Margins may be estimated by: a macroscopic examination (intraoperative consultation), reviewing images, Faxitron analysis, touch imprint cytology, intraoperative frozen section examination, radical method (perpendicular margin), shave method (parallel to the margin) and cavity walls shaving after quadrantectomy. No generally accepted definition of an adequate negative surgical margin after conserving surgery exists, but most authors agree with the most recent recommendations that a negative margin implies "no ink on tumor" in histological preparations. There are cases in which a margin wider than "no ink on tumor" was indicated for invasive breast cancers, as well as a width less than 2 mm for DCIS patients. Each pathological finding after surgical treatment of breast cancer must contain the margin status [17,21]. Multifocal tumors are defined as multiple invasive carcinoma foci localized in the same breast quadrants. The procedure in this situation in everyday clinical practice was tested by asking the following question: "What would you do if a patient had multifocal tumors which responded well to NAT?". The majority of surgeons (78%) opted for BCS, 11% for mastectomy, whereas the remaining 11% would reach a decision for each patient individually.

Multicentric tumors are defined as invasive tumors in different quadrants of the same breast. In this case, the experts had different opinions: only 20% of surgeons would opt for BCS, 40% would not take BCS into consideration, 40% would opt for BCS depending on the response to NAT and 30% provided the margins were clean and the radiotherapy of the whole breast was planned (it was possible to choose multiple answers).

This group of experts concluded that multifocal tumors may be treated with BCS in most cases, whereas mastectomy is proposed for multicentric tumors, except in special cases of a very good response to NAT, only in reference centres with mandatory radiotherapy of the rest of the breast after BCS.

It is highly important to enable access to oncoplastic procedures to patients, primarily subcutaneous mastectomy with or without preserving the areola and mamilla ("nipple areola complex"; NAC) with immediate or delayed reconstruction. It is necessary to include a plastic-reconstructive surgeon or oncologic surgeon trained for oncoplastic surgery in the team. The type of reconstruction must be thoroughly discussed in the MdT with a necessary consent of the patient. Moreover, the time and location of radiography after subcutaneous mastectomy need to be discussed.

The most discussed topic related to surgery after NAT was the one related to SLNB, especially if positive axillary lymph nodes (cN+) were clinically and/or radiologically diagnosed prior to NAT. At the initial voting, 67% of surgeons opted for a complete dissection of the axilla (axillary lymph node dissection – ALND) if lymph nodes were positive prior to the onset of treatment; 22% opted for SLNB, whereas 11% would go with SLNB, provided that at least three lymph nodes are identified and examined.

NSABP B-27 is the first study to present SLNB results in patients with positive axillary lymph nodes prior to NAT. In this study, SLNB was done prior to ALND in 428 (18%) out of a total of 2411 patients; 23.8% of them had positive lymph nodes prior to NAT. The false-negative rate of SLNB in this study was 10.7% and there were no differences in patients with negative or positive lymph nodes prior to NAT. Similar results were obtained by a French study with a significantly smaller number of patients. The percent of false-negative SLNB did not differ in clinical N+ and N- cases (15 and 9.4%, respectively; p=0.66) [22]. The MD Anderson Cancer centre study [23] encompassed 150 patients with a biopsy-confirmed N+ status of the axilla. SLNB was performed in a total of 111 patients, the rate of SLN identification was 93%, with a false-negative rate of 20.8% after ALND. The study concluded that ALND was the standard treatment in patients with N+ prior to NAT. Sentinel Neoadjuvant Trial (SENTINA) [24] is a study which included 1737 patients and divided them into four groups. Group A (n=662) included patients with clinical/radiological N- axilla prior to NAT who remained N- to SLNB prior to NAT. Group B (n=360) was comprised of patients who were N+ to SLNB prior to NAT. In these patients, SLNB was done again after NAT, followed by ALND. Group C (n=592) involved patients with clinical/radiological N+ axilla (N+ was pathologically confirmed in 149 of these patients) in whom axillary lymph nodes became clinically negative after NAT. Finally, group D (n=123) encompassed

patients with clinical N+ axilla both prior to and after NAT, in whom ALND was done. SLNB after NAT in group B led to a low rate of SLN identification (60.8%) and a high rate of false-negative SLN (51.6%). Also, the identification rate was relatively low in group C (80.1%), with false-negative SLN in 14.2% of cases. The false-negative rate of SLN was lower if three or more SLNs were identified and if double marking was used (technetium and vital dye) [24-26]. Several subsequent studies demonstrated that the rate of false-negative SLN was less if three or more SLNs were identified, with the comment that a great number of lymph nodes could not be identified in most of the patients [20-30]. On the other hand, several studies with clinical N- patients showed that the identification rates of SLN and false-negative SLN were equal to SLNB rates after surgery without NAT. Therefore, they reached a uniform conclusion that this type of treatment could be safely applied [22,27,28,31].

The panel has discussed this issue and concluded that SLNB is safe in N- patients prior to NAT, whereas SLNB in N+ patients has certain limitations.

First of all, it is necessary to diagnose N+ adequately. In case of clinical suspicion of N+, it is necessary to perform an ultrasound examination of the axilla and if possible – FNA or SLN biopsy of the suspicious lymph node.

After an accurate diagnosis of N+, the conclusion of the project participants is the following:

SLNB is allowed in patients with N1, whereas in patients with N2 it is allowed only if a good clinical or radiological response to NAT has been achieved. It is recommended to perform this procedure in reference centres, with double marking, and, if possible, with isolating three or more axillary SLNs. However, axillary dissection remains a rational option in N+ patients, either N1 or N2.

This is in accordance with the opinion of a group of experts in St. Gallen in which 90% of the participants declared that SLNB was an adequate method after NAT and a successful downstaging of axillary lymph nodes [21].

Radiotherapy after NAT

The expert panel is completely in accordance with the recommendations of the National guide for breast cancer diagnosis and treatment to perform radiography after the completed NAT according to tumor characteristics prior to NAT, regardless of the response to the administered NAT [1].

Most experts of the Gt. Gallen board agree with this view, compared to the view that radiography is performed according to tumor characteristics after NAT (68 and 24%, respectively) [21].

NAT combinations

Neoadjuvant chemotherapy should be administered according to the National guide for breast cancer diagnosis and treatment [1]. Applied therapeutic regimens correspond to those which are used in the adjuvant treatment of breast cancer.

Special emphasis has been put on the fact that the entire planned NAT must be completely applied prior to surgery, not partly after surgery.

ESMO recommended the same [17]

In HER2 positive breast cancer, four cycles of anthracycline chemotherapy followed by taxane therapy concomitantly with four cycles of trastuzumab is the standard of treatment according to the National guide for breast cancer diagnosis and treatment [1].

Since its publication in 2013, there have been new conclusions regarding NAT of HER2 positive breast cancer.

Dual anti-HER2 therapy with trastuzumab and lapatinib in the NeoALLTO study led to a considerably higher rate of pCR compared to monotherapy with trastuzumab or lapatinib [32].

However, since it did not affect DFS and OS [33], ESMO does not recommend this type of NAT [17].

The authors of the NeoPULSE project do not support the combination of trastuzumab and lapatinib as a regimen for NAT of breast cancer.

The TRYPHAENA study examined the effect of dual HER2 blockade with trastuzumab and pertuzumab in combination with different chemotherapy regimens. In the first group, dual blockade was combined with the combination of docetaxel and carboplatin, in the second one trastuzumab and pertuzumab were combined with docetaxel after four cycles of anthracycline regimen, and in the third group, dual blockade was administered concomitantly both with anthracycline regimen and docetaxel. pCR was over 54% in all three groups, with the highest pCR rate in the group with docetaxel and carboplatin - 63.6% [34].

In the NeoSPHERE study, dual HER2 blockade with trastuzumab and pertuzumab in combination with docetaxel resulted in a pCR rate of 45.8% as compared to 29.0% and 26.0% when docetaxel was combined only with trastuzumab, i.e. pertuzumab.

When asked whether the results of the Neo SPHERE study had practice changing significance, most of the oncologists (80%) and surgeons (78%) from the NeoPULSE project answered affirmatively.

Based on these data, the authors have concluded that the administration of dual HER2 receptor blockade with trastuzumab and pertuzumab along with chemotherapy in the neoadjuvant approach

is a desirable therapeutic option, particularly in patients with a high risk of recurrence.

A similar recommendation on the use of dual blockade with pertuzumab and trastuzumab has been given by ESMO, NCCN and St. Gallen conference [2,17,21].

In TNBC, after the administration of common anthracycline/taxane regimens, the pCR rate is around 30%, whereas the addition of carboplatin increases pCR rates [19,35].

In the GeparSIXTO study [19,20], the addition of carboplatin to standard therapy led to a pCR rate of 53.2% in TNBC, and 61.5% in BRCA+ patients. This was reflected in a longer three-year DFS (85.8 and 76.1%, respectively). However, in the CALGB40603 study, regardless of a considerably higher pCR rate with the addition of carboplatin, DFS wasn't longer in this group of patients [35].

Given the inconsistent results of the studies, the authors consider that platinum derivates are not indicated in NAT of TNBC. The application of platinum agents could be considered in BRCA+ patients.

The role of hormone therapy in NAT has also been discussed.

The experts concluded that hormone therapy is possible only in patients with non-operable tumors which are not suitable for chemotherapy. The length of the administration should be at least 4-6 months.

According to current opinions, postoperative chemotherapy, after preoperative NAT has been completed, is not routinely indicated.

However, some project participants believe that non-cross-resistant adjuvant chemotherapy regimens should be considered in high-risk patients.

A study that dealt with this issue, CREATE-X, presented its results at the San Antonio Breast Cancer Symposium in December 2015 [35]. In this Japanese study, patients received standard neoadjuvant chemotherapy for HER2- breast cancer. Patients who did not achieve a pCR were randomized to 8 cycles of capecitabine treatment or follow-up, i.e. continuation of hormone therapy for HR+. The study showed benefits of capecitabine addition regarding a 5-year DFS (74.1 vs 67.7%, p=0.005) and OS (89.2 vs 83.9%, p<0.01).

The experts concluded that adjuvant hormone and/or HER2 targeted therapy should be continued after surgery in patients with HR positive and HER2 positive breast cancer, regardless of the response to the administered NAT.

The administration of non-cross-resistant adjuvant chemotherapy may be considered in high-risk TNBC patients who did not achieve a pCR after NAT.

A similar strategy is applied at the Oncology Institute of Southern Switzerland (IOSI), where adjuvant chemotherapy is administered only in TNBC N+ patients after NAT, without the achievement of a pCR. In these patients at IOSI, cyclophosphamide-methotrexate metronomic therapy is administered for a year, whereas in patients with HR+ and HER2+ breast cancer standard adjuvant therapy and trastuzumab therapy without chemotherapy are administered, respectively [37].

The project participants also consider that it is necessary to retest the receptor status (ER, PR, HER2, Ki67) after NAT.

This is especially significant in cases when some of the receptors are negative prior to NAT. Moreover, all surgeons and medical oncologists who participated in the project agree that therapy should be conducted following the "one positive receptor" principle, i.e. if HER2 receptor is positive in at least one analysis (either preoperative or postoperative), trastuzumab therapy should be administered for up to a year, that is, hormone therapy in case HR is positive in at least one histopathological finding.

Education

According to the number of newly-diagnosed cases of breast cancer, Serbian results correspond to the European average. However, according to the number of breast cancer deaths, Serbia occupies the second place in Europe. Breast cancer mortality in the European Union (EU) is 22.4/100.000, whereas in Serbia it amounts to 31.5/100.000.

In other words, chances for a woman living in Serbia to die from breast cancer are 40% higher than for a woman living in the EU [37]. A possible explanation for such disturbing statistics lies in the lack of systemic screening, shortage of radiotherapy equipment, but also in the unavailability of some newer drugs. Insufficient education of doctors in this field has been identified earlier, as well as insufficient health education of women.

Education at all levels may change this situation, therefore, it is necessary starting from undergraduate medical students' studies. Namely, there is a clear discrepancy between breast cancer epidemiology and the number of classes at the university which deal with this issue. Moreover, the education of general practitioners who are often the first to examine patients is also unsatisfactory and has to be conducted with a focus on early breast cancer diagnosis and adequate patient follow-up after treatment. Better education is also necessary in the course of different residency programs, during which residents usually lack good education in this regard.

We hope this paperwork will contribute to the education of surgeons, medical oncologists, radiologists, radiotherapist and pathologists who deal with breast cancer treatment both in secondary and tertiary healthcare institutions, i.e. reference centres. Further educational activities are going to include themed educational meetings with a focus on establishing the uniformity of diagnosis and treatment of breast cancer in Serbia.

Conclusion

Decisions on the treatment of breast cancer patients should be in accordance with worldwide accepted recommendations on the treatment and apply uniformly in entire Serbia.

Decisions on the treatment should be reached by a MdT which has to include doctors of different oncology specialties with experience in breast cancer treatment.

Education on breast cancer diagnosis and treatment has to be carried out continuously.

Summary of conclusions

- No decisions on the treatment of breast cancer patients should be reached outside an MdT.
- Histopathological result, as well as biological characteristics of breast cancer (ER/PGR/HER2/Ki67), should be determined prior to reaching a decision on the treatment in more than 90% of patients with invasive and 85% of patients with non-invasive breast cancer.
- Histopathological and IHH tumor results should be obtained by core needle biopsy before treatment, whereas the results of patients with N+ should be supplemented with fine needle aspiration (FNA) biopsy of axillary lymph nodes or SLNB.
- SLNB may be done during surgical treatment in patients with clinically negative axillary lymph nodes (N-) before the administration of NAT.
- NAT could be considered for T2 tumors as well, if breast conserving surgery is planned.
- Chemotherapy combinations for NAT are the same as for adjuvant therapy (ACx4, sequentially with taxanes). The entire chemotherapy (HT) must be completed preoperatively.
- Postoperative HT after the completed NAT is not indicated.
- HER2 positive breast cancer (T2) is the indication for NAT, therefore anti-HER2 therapy needs to be part of the treatment in NAT (should not be combined with anthracyclines, only with taxanes).
- The administration of dual HER2 receptor blockade with trastuzumab and pertuzumab along with chemotherapy in the neoadjuvant setting should be optional in patients with a high risk of recurrence.
- In TNBC, NAT is currently the same as for other breast cancer subtypes.
- In luminal A-like tumors, the administration of endocrine NAT is indicated only in special situations (comorbidity that contraindicates chemotherapy, patient's choice).
- BCS could be feasible after NAT.
- BCS is not contraindicated for carefully selected patients with muctifocal tumors.
- Mastectomy is usually performed in patients with multicentric tumor, except for individual cases of a very good response to NAT, only in reference centres with mandatory postoperative radiotherapy after BCS.
- Patients should be offered oncoplastic procedures.
- Histopathological assessment of tumor response after NAT is mandatory.
- pCR should be defined as ypT0N0.
- Retesting of the receptor status ER/PR/HER2 as well as Ki67 after NAT is advised.
- After surgery, postoperative anti-HER2 therapy is mandatory up to a year from the first dose within NAT.
- Adjuvant endocrine therapy is mandatory for patients with breast cancers expressing ER/PR following recommendations for adjuvant endocrine therapy.
- The administration of non-cross-resistant adjuvant chemotherapy may be considered in high-risk TNBC patients who did not achieve a pCR after NAT.
- All therapeutic options and treatment plans must be clearly communicated to patients and patients must give their written consent.

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Conflict of interests

The authors declare no conflict of interests.

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