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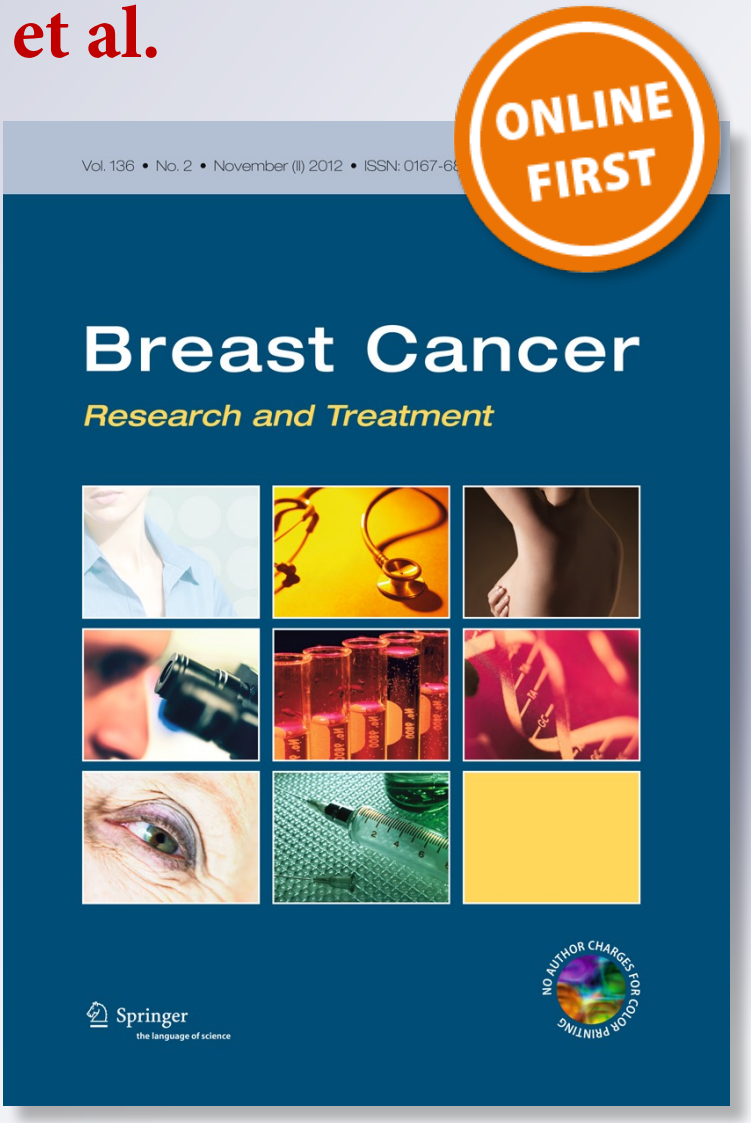

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BRIEF REPORT

Preoperative systemic therapy in locoregional management of early breast cancer: highlights from the Kyoto Breast Cancer Consensus Conference

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Abstract Data reviewed at the Kyoto Breast Cancer Consensus Conference (KBCCC) showed that preoperative systemic therapy (PST) could optimize surgery through the utilization of information relating to pre- and post-PST tumor stage, therapeutic sensitivity, and treatment-induced changes in the biological characteristics of the tumor. As such, it was noted that the biological characteristics of the tumor, such as hormone receptors, human epidermal growth factor receptor-2, histological grade, cell proliferative activity, mainly defined by the Ki67 labeling index, and the tumor's multi-gene signature, should be considered in the planning of both systemic and local therapy. Furthermore, the timing of axillary sentinel lymph node diagnosis (i.e., before or after the PST) was also noted to be

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critical in that it may influence the likelihood of axillary preservation, even in node positive cases. In addition, axillary diagnosis with ultrasound and concomitant fine needle aspiration cytology or core needle biopsy (CNB) was reported to contribute to the construction of a treatment algorithm for patient-specific or individualized axillary surgery. Following PST, planning for breast surgery should therefore be based on tumor subtype, tumor volume and extent, therapeutic response to PST, and patient preference. Nomograms for predicting nodal status and drug sensitivity were also recognized as a tool to support decision-making in the selection of surgical treatment. Overall, review of data at the KBCCC showed that PST increases the likelihood of patients receiving localized surgery and individualized treatment regimens.

Keywords Breast cancer · Preoperative systemic therapy · Sentinel lymph node · Breast-conserving therapy

Introduction

Preoperative systemic therapy (PST) is the current standard of care for locally advanced breast cancer and stage II patients who may not be immediately suitable for breast-conserving surgery (BCS). Recent clinical trials have demonstrated that survival outcomes for patients who received PST are similar to those who received the same treatment postoperatively [1]. Furthermore, monitoring the tumor response to PST can allow for the selection of both systemic and surgical treatment according to individual patient disease characteristics. Indeed, surgical options, as localized treatment following PST should be considered based on the post-PST status of the tumor volume. The timing of sentinel lymph node (SLN) diagnosis (i.e., before or after PST) is also an important issue for consideration in the locoregional management of early breast cancer, as is the use of predictive biomarkers for the response to PST and nomogram/algorithms to estimate the tumor spread. In addition, information regarding tumor response and behavior following PST will help further understanding of tumor biology. In this article, we present a summary of discussions from the 2nd Kyoto Breast Cancer Consensus Conference (KBCCC) regarding the role of PST in the management of early breast cancer, which indicated that PST increases the likelihood of patients receiving localized surgery and individualized treatment regimens [2].

Purpose of preoperative systemic therapy

PST has a number of purposes in the treatment of primary breast cancer, including permitting the option of BCS for patients who may otherwise have required total mastectomy, and monitoring of the therapeutic response to this treatment. However, it is unclear whether PST is considered for patients who do not opt for BCS. Indeed, PST could also be considered as a treatment option for patients who are unlikely to achieve BCS after PST, as it provides information regarding drug sensitivity. PST may also be recommended for patients who have a family history of breast cancer, including BRCA genetic mutations; knowledge of therapeutic sensitivity could be beneficial in the subsequent treatment of these patients [3]. However, patient preferences must be factored into the clinical decision-making process.

Data are now available on the rates of local recurrence after PST, including findings from the National Surgical Adjuvant Breast and Bowel Projects (NSABP) B-18 and B-27. There was some evidence from B-18 of a doubling of local recurrence rates among patients that underwent wide local excision and who initially required a mastectomy, however, when all BCS cases were included from the analysis, the recurrence rates were similar at the 16-year follow-up (approximately 7.7 vs. 9.9 %). It is worth noting

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that the addition of taxanes to the B-27 study regimen increased the pathological complete response (pCR) but did not improve overall BCS rates [1].

According to the NSABP B-27 study, clinical non-responders to anthracycline did not derive any survival advantage from addition of a taxane to the treatment regimen [1], while clinical responders showed increased pCR rates and increased survival. These data all suggest that cross-resistance/sensitivity mechanisms might exist, even though the pCR rates and survival benefits do not appear to demonstrate cross-resistance in vitro.

Recent studies have demonstrated that pCR rates induced by multi-drug cytotoxic chemotherapy tend to be highest in rapidly proliferating tumor subtypes, such as in the non-luminal human epidermal growth factor receptor-2 (HER2) type and triple negative diseases [4, 5]. It is unlikely that pCR will be achieved in luminal-type A diseases that are not characterized by rapid cell proliferation [6]. However, no established biomarkers currently exist to predict tumor responses to specific chemotherapeutic agents, which represents therapeutic and research challenges in the translational study of breast cancer. In particular, persisting critical issues for targeted therapies include the selection of patients that could respond to PST and the prediction of survival outcomes (i.e., disease-free and overall survival).

Biological features of tumors and response to systemic therapy

In the subgroups of non-luminal HER2 type and triple-negative cancers, patients who achieved pCR following preoperative chemotherapy were usually associated with more favorable prognoses compared to patients without pCR [5, 7–10]. In addition, patients that became axillary node negative following PST had significantly better prognoses compared with patients that remained node positive [11]. This finding may also apply to patients with luminal-type B disease. Although the definition of luminal-type A and B and the criteria for pCR varied among investigators, a large number of attempts to select systemic treatment based on individual tumor biology, with the aim of increasing pCR rates, have been reported. Indeed, several methods designed to distinguish between luminal-type A and B are currently available, including the most promising and widely applicable Ki67/MIB1 labeling index (Ki67LI) and/or multi-gene assays (e.g., PAM50, Oncotype DX® and Mammaprint®), together with the assays to evaluate ER and HER2 status and the histologic grade of the tumor. Efforts are also underway to clarify tumor subtypes using multiple biological parameters; most of the methods for multi-gene profiles introduced in the market are linked to genes associated with the cellular proliferative and invasive activity of a tumor [12]. As the downregulation of cell proliferation often results in tumor response and favorable survival outcome [13], it is important to sequentially monitor the tumor phenotype, for markers of cell proliferation, before and after PST. In particular, the biomarker status of tumors is changed by treatment in some cases [14, 15]. As a result, increased numbers of biomarkers involving basal tumors, BRCAness, the PI3KCA/AKT, mitogen-activated protein kinase pathway and mTOR are likely to be intensively examined in the coming years [16–19].

Assessment of tumor volume and tumor extent before and after PST

Objective evaluation of the pretreatment status with respect to tumor volume and tumor extent, including potential multifocality of any apparent unifocal lesions and nodal involvement, is critical in the use of PST for the locoregional management of early breast cancer. Mammography, ultrasound (US), and magnetic resonance imaging (MRI) are in general useful for monitoring tumor response to treatment. The maximum diameter of a tumor, its volume, and contrast kinetic patterns could be evaluated using MRI. MRI is currently the most sensitive tool for detecting intraductal components or small residual tumors after chemotherapy. However, it should be noted that MRI tends to detect false-positive lesion(s) and may increase mastectomy rates by over-estimating the extent of the intraductal component. Nonetheless, it is useful for monitoring treatment-induced changes, especially tumor volume shrinkage from a quantitative aspect [20–22]. Additional MRI-guided biopsies may be necessary in some circumstances for evaluation of additional lesions detected on MRI alone (limited specificity) and these further biopsies may help reduce unnecessary mastectomies.

Tumor shrinkage generally encourages patients to continue with their scheduled systemic treatment. Marked clinical responses increase the probability of pCR, particularly in those tumors with biological features that are associated with pCR [1]. Approximately half to two-thirds of patients with a complete clinical response will have a pCR and one-third of patients with a pCR will have radiological evidence of a residual tumor. Therefore, relying on the combination comprising the biological characteristics of the tumor and the clinical therapeutic response tends to increase the predictive accuracy for pathological response [23, 24]. Recently, several studies have shown that dynamic MRI or PET-CT scan after the 1st or 2nd cycle of PST can provide additional information for predicting pathological tumor response to conventional factors [25, 26]. In addition, serial tumor biopsies can be incorporated into protocols to increase understanding of treatment-induced changes to the tumor biology. Tumor

regression and shrinkage patterns in response to PST should be analyzed in relation to tumor subtype, rates of BCS and local control rates after surgery [27–29].

Assessment of pathological response

As pathological assessment of the tumor response can predict survival outcomes, it is important that competent, board certified pathologists working in accredited institutions evaluate the tumor specimens. Thorough sectioning of the resected specimens is mandatory to determine pathological response. In the majority of cases, the examination based on hematoxylin and eosin-stained slides is considered sufficient; however, additional immunohistochemical evaluation with pan-cytokeratin, cytokeratins 5/6 and p63 may be required occasionally, to precisely confirm the presence or absence of tumor cells and the non-invasive nature of carcinoma cells. For the remaining cancer cells, examination of Ki67LI should be also considered.

Multiple classification systems, for assessment of the pathological response, have been reported in the literature [30, 31]. The absence of invasive tumor in the breast (pNoninv) and macro/micrometastases or isolated tumor cells in the axillary nodes has been commonly used to define pCR following PST. However, other criteria have been also used, such as pTotal (no tumor cells remaining). The criteria for assessing pathological response must be clearly enunciated along with monitoring of quality control and assurance within each institution. Immunohistochemical evaluation must be performed to insure that there are no residual carcinoma cells after the therapy as described. Most classifications have been developed in relation to cytotoxic chemotherapy and it might be necessary to also develop a methodology to confirm pCR for preoperative anti-HER2 containing therapy. Tumor biological features may change in response to the modes of treatment. For instance, the short-term changes in Ki67LI over a two-week period are predictive of longer-term survival outcomes in endocrine treatment [32, 33]. Low levels of KI67 expression following PST are a predictor of a favorable prognosis. There are other investigational parameters related to the immune system and tumor angiogenesis, which are potential components of therapy-induced biological changes [34].

Breast surgery

The original tumor volume and extent, biological features and therapeutic response are three major factors that influence decision-making for breast surgery after PST (Fig. 1). For instance, a triple-negative tumor with a well-defined margin before PST and an excellent clinical response consistent with concentric shrinkage may be treated with limited resection after PST, if negative surgical margins are attainable. For luminal-type tumors, especially type B, a different treatment approach may be required because the likelihood of achieving pCR varies between individuals and the overall pCR rate is modest [35, 36]. At the KBCCC, it was elucidated that the surgical procedure and precise resection volume should be based on both pre-and post-PST tumor volume and extent for luminal-type tumors, while for non-luminal tumors it should be planned according to post-PST tumor status. For clinical CR cases with non-luminal tumor subtype, very limited resections tended to be performed. Intraoperative identification of residual tumors may be difficult. Microclip placement, tattooing, and photographs are quite useful for localizing the tumor after treatment with chemotherapy.

In terms of prediction of response, Ki67LI might be useful for determining the probability of pCR (e.g., low proliferative activity may relate to less chemo sensitivity), however, local quality control of the assay needs to be performed routinely and cut-points need to be carefully considered for each endpoint. In addition, high scores by multigene assays would be helpful for predicting pCR in luminal subtypes [37]. Radiotherapy cannot be omitted and cannot substitute for surgery in the majority of the cases; this is associated with doubling of local recurrences. According to recent studies, the effectiveness of radiation therapy for local controls differs between luminal and non-luminal disease subtypes [38]. For planning surgical margins, different radiosensitivity among different subtypes must be considered.

Axillary surgery

Definitive axillary treatment should be based on the initial nodal status. US-guided fine needle biopsy/CNB is useful for the identification of nodal metastasis, particularly macrometastasis, before performing SLN biopsy (Table 1; Fig. 2). SLN biopsy can be considered prior to PST for clinically node negative patients and those with a negative needle nodal biopsy, because the patients would have a reasonably high chance of axillary preservation.

When SLN biopsy is performed before PST, surgical treatment of the axilla can be guided according to the recommendations shown in Table 2. Although it is necessary to discuss with the patients the uncertainty of metastasis in para- or non-SLNs for those patients with a positive SLN, axillar lymph node dissection (ALND) can be individualized in those cases with micrometastasis or limited macrometastatic involvement e.g., metastatic ratio <50 % (number of metastatic nodes/number of examined nodes). The tumor response and other factors, such as age, need to be taken into account in this situation [39–41].

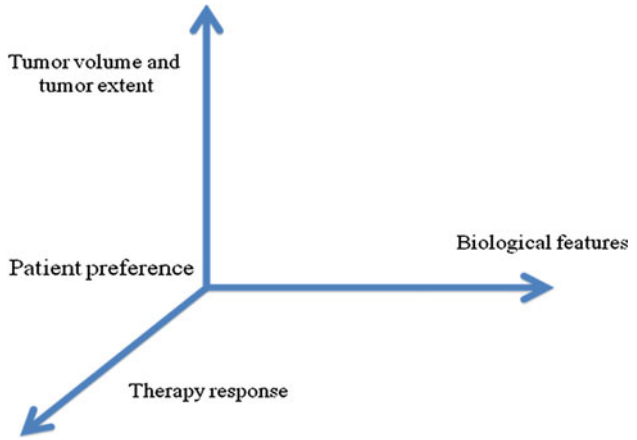


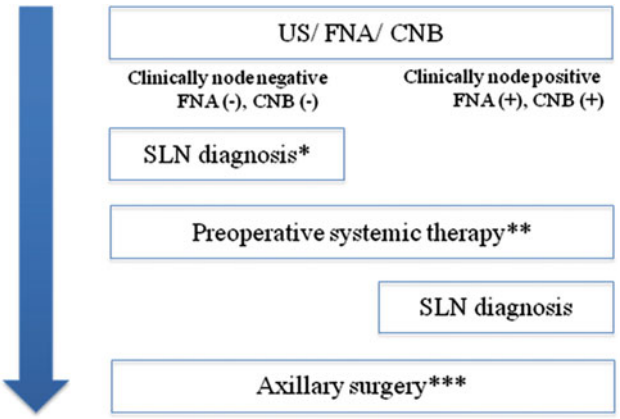
Fig. 1 Decision-making for local therapy after PST

Table 1 Axillary diagnosis, sentinel lymph node biopsy

Subject	Points of discussion and remarks
Indication of SLN biopsy	SNB is not contraindicated for surgery of "high-risk DCIS" (e.g., high-grade DCIS with comedo necrosis)
	SLN biopsy should be appropriate for extensive and/or high-grade DCIS requiring mastectomy
	SLN biopsy is a standard of care for staging the axilla in clinically node-negative invasive breast cancer patients with T0-3, and with multifocal/multicentric tumors
Method of SLN biopsy	Blue dye and radioisotope (RI) method is a gold standard in the method
	Several new methodologies, such as indocyanine green fluorescence (ICGf) method, are used in common practice locally
Axillary ultrasound (US) diagnosis	Diagnostic sensitivity increases depending on increase in tumor size
	Cortex thickness (e.g., >2.5 mm) helps to predict nodal metastasis
	Usefulness of intraoperative US diagnosis in detecting non-SLN is under investigation
FNA cytology/CNB	False-positive rate of FNA would be around 2 %
	False-negative rates of FNA increase depending on the decrease in the number of involved nodes
	If FNA or CNB positive, SLN biopsy could be unnecessary
	If FNA or CNB negative, SLN biopsy should be considered

Several issues on axillary diagnosis were summarized

If SLN biopsy is conducted after preoperative chemotherapy, it is reasonable to infer that any remaining tumor cells within the axillary nodes are resistant to therapy,



*ACOS Z11 could be taken into account if node-positive.

** Tumor response should be considered. Residual tumors are resistant to the treatment generally.

*** Nomogram / mathematical algorithm are used occasionally.

US: Ultrasound, FNA: fine needle aspiration, CNB: Core needle biopsy

Fig. 2 Algorithm of axillary management for PST. *ACOSGZ0011 could be considered if node-positive. **Tumor response should be considered. ***Mathematical algorithm are used occasionally. *US* ultrasound, *FNA* fine needle aspiration, *CNB* core needle biopsy

Table 2 Axillary lymph node dissection before and after PST

Nodal status	Completion of ALND
SLN diagnosis before PST	
Node negative including ITC*	Not recommend
Micrometastasis[a] or limited macrometastasis[b]	Individualized (Other factors have to be taken into account to avoid ALND[c])
Other node positive	Recommend
SLN diagnosis after PST	
Node negative including ITC	Avoidable (Other factors have to be taken into account[c])
Micrometastasis or limited macrometastasis	Recommend (No data support the avoidance, but worthwhile for investigation)
Other node positive	Recommend

ITC isolated tumor cells

[a] Micrometastasis: size of metastasized tumor is 200 μm–2 mm

[b] The metastatic rate, number of positive nodes/number of examined nodes, <50 %

[c] Total mastectomy or partial mastectomy, multifocality, subtype, lymphatic invasion and tumor response (after PST)

therefore, ALND would be indicated. If micrometastases are only evident after PST, ALND should be recommended; however, clinical trials investigating omission of ALND in these circumstances are warranted. If there are residual SLN metastases post-PST, these are partially or wholly resistant to chemotherapy and the same is presumably true of non-sentinel nodes. Patients do not usually

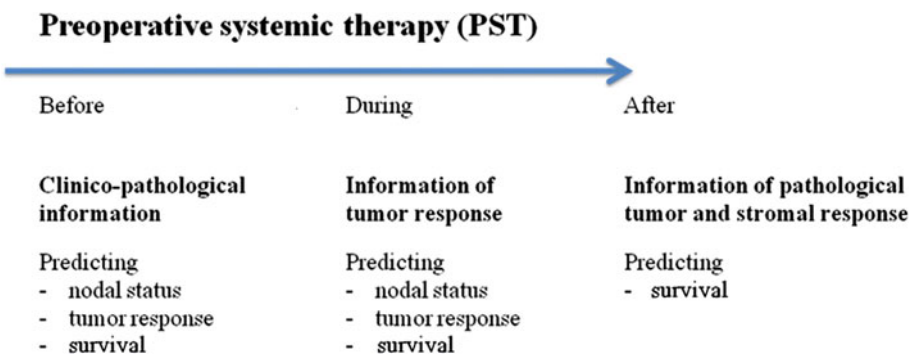


Fig. 3 Nomogram/algorithm before, during, and after PST

receive any further chemotherapy, but may receive adjuvant systemic hormonal therapy, which could further downstage non-sentinel nodes in node-positive disease if completion ALND is not undertaken. At the KBCCC, there was some hesitation in recommending ALND when there was a clinical CR. This would apply to patients undergoing *either* mastectomy or BCS.

Axillary management, including indications and methodology for SLN biopsy, is summarized in Table 2. It is possible to perform a repeat SLN biopsy after PST, and this is being explored in the German SENTINA trial. Intraoperative US examination is a potential technique for identifying metastases in non-SLNs.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial is a phase 3 non-inferiority trial that compared observation only with completion ALND in breast cancer patients with T1–T2 tumors and no palpable axillary lymph nodes [42]. No significant differences in loco-regional control or disease-free survival were noted between the two groups at a median follow-up of 6.3 years. Patients with 1 or 2 SLNs (i.e., </= 3) containing macro- or micrometastases who underwent BCS followed by radiation therapy and systemic therapy were randomized to observation or completion ALND. It was therefore suggested that non-PST patients who met the Z0011 trial conditions could have a chance of omitting completion ALND.

Nomograms and algorithms

Nomograms and algorithms are being increasingly used in breast oncology clinics, to provide information for patients and providers, standardize treatment, and provide tools for informed selection of treatment. Specific examples include tools for the prediction of pathological response to PST, estimation of the number of involved nodes, and the presence or absence of metastasis in non- or para-SLNs. For PST, nomograms and algorithms should be used in conjunction with clinical information, such as tumor response rates in a pathway of treatment as shown in Fig. 3. In a case study discussed at the KBCCC (2011), it became apparent that information from nomograms or other mathematical model predictions could significantly influence clinical decision-making. In particular, when treatment decisions may depend on quality-of-life considerations, or if there is a trade-off between treatment toxicity and subsequent delay in disease progression, decision-making may be aided by a nomogram that shows the expected quality-adjusted time gained (or lost) according to different valuations that patients may place on the time spent experiencing treatment toxicity and the time spent following disease progression [43]. It is important to improve the predictive accuracy of these nomograms and algorithms in prospective clinical trials and better define indications for their clinical use. As described at the KBCCC (2011), accuracy may be improved through the use of meta-analysis and other methods for pooling data from multiple studies.

Conclusions

Review of PST shows that information relating to tumor status, biological characteristics, and therapeutic responses must be integrated to formulate decisions regarding surgery and other treatment procedures. Furthermore, the timing of SLN biopsy, before PST or after PST, can be individualized for each patient according to nodal status at presentation. Incorporation of nomograms or mathematical algorithms into clinical practice is a worthwhile area of study that requires further investigation.

Discussants and local organizers

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Conflict of interest None.

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