Current Trends and Controversies over Pre-operative Chemotherapy for Women with Operable Breast Cancer

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The multi-disciplinary approach, including surgery, chemotherapy, endocrine therapy and radiation therapy, has become the standard treatment for primary breast cancer patients. The indication of pre-operative chemotherapy has been extended to women with potentially operable breast cancer based on the results of large randomized studies and has become an attractive option that extends the chance of breast conservation. The clinical and pathological responses to pre-operative chemotherapy correlates with long-term outcome. The anthracycline-containing regimen is now considered the standard. Sequential administration of non-cross-resistant drugs, namely taxanes, improves local tumor response but its long-term benefit has been controversial. Prediction of response to pre-operative chemotherapy still remains a challenge. Identification of useful predictive markers and development of molecular-targeted drugs is the key to individualized therapy in the future.

Key words: pre-operative chemotherapy — breast cancer — advantage — response — long-term outcome — prediction

INTRODUCTION

The multi-disciplinary approach, including surgery, chemotherapy, endocrine therapy and radiation therapy, has become the standard treatment for primary breast cancer patients with a high risk of recurrence. Although mortality from breast cancer is decreasing in western countries thanks mainly to early detection of the disease by mammography screening and wide usage of post-operative adjuvant systemic therapy (1), its incidence and mortality are steadily increasing in the rest of the world, including Japan (2).

When it first emerged in late 1970s, the use of pre-operative (primary) chemotherapy had been primarily limited to women with inoperable locally advanced breast cancer to enable optimal local therapy (3–5). Later on, large randomized trials proved that pre-operative chemotherapy has at least the same survival benefit as the post-operative chemotherapy (6), and its indication has been extended to women with potentially operable breast cancer.

However, with long-term survivors increasing by systemic therapy in early breast cancer, the ‘survivorship’ or importance of quality of life after primary therapy has recently come into the limelight. Whether an attempt at breast conservation can be made at the time of definitive surgery is one of the important issues discussed among patients and physicians. Pre-operative chemotherapy is an attractive option for those who have large tumors but a strong interest in breast conserving surgery.

In this review, we describe available evidence and discuss current controversies and future prospects of pre-operative chemotherapy, taking account of its two major clinical roles; eradication of micrometastasis and increased chance of breast conservation.

RATIONALE OF PRE-OPERATIVE CHEMOTHERAPY

Biologic rationale for pre-operative adjuvant chemotherapy was derived from the pre-clinical studies in animal models. It had been known that growth kinetics of metastatic tumors change after surgical removal of the primary lesion (7). The greatest effect of chemotherapy was observed when it was administered prior to operation (8, 9). These observations led to a hypothesis that early systemic chemotherapy prior to surgery might further reduce the risk of metastasis.

The landmark trial in a clinical setting was the National Surgical Adjuvant Breast and Bowel Project (NSABP)
B-18 trial, which showed pre-operative chemotherapy for operable breast cancer by doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² (AC) was at least as effective as post-operative adjuvant chemotherapy with the same regimen in terms of disease-free and overall survival (10). The results were consistent over a longer follow-up period (6) and the result of another large randomized trial conducted in Europe was also confirmatory (11). A recent meta-analysis of pre-operative and post-operative chemotherapy (partly including T4 disease) indicated that pre-operative chemotherapy was equivalent to post-operative therapy in terms of survival and disease progression (12).

Thus the available clinical data has not demonstrated a convincing difference in long-term outcome as hypothesized in pre-clinical studies. However, a higher proportion of women were able to undergo breast conservation surgery. In addition, because the extent of clinical and pathological responses to pre-operative chemotherapy correlates with survival (10), improved tumor response in this setting is expected to improve the overall outcome.

ADVANTAGE OF PRE-OPERATIVE CHEMOTHERAPY

The advantage of pre-operative therapy is that one can subjectively evaluate the response to systemic therapy in vivo. Both clinical and pathological responses have been associated with prolonged disease-free and overall survival (6, 8) and they are used as the primary endpoint in clinical trials. Unlike post-operative adjuvant chemotherapy, one can avoid or minimize the unnecessary toxicities from cytotoxic agents by changing treatment strategy when the tumor is not responding to a certain regimen.

Pre-operative chemotherapy is an attractive option for women who wish to reduce the extent of local surgery. Clinical trials provide evidences that 28–89% of women can undergo breast conserving surgery when they might not be otherwise qualified (12).

Because breasts are located on the body surface, one can easily obtain the tumor cells or tissue by either fine needle aspiration or core needle biopsy with minimal invasions. As one can also evaluate the response to systemic therapy in a subjective manner and because patients are usually chemotherapy naïve, a pre-operative setting can be an ideal in vivo laboratory for biomarker studies using tumor specimens.

DISADVANTAGE OF PRE-OPERATIVE CHEMOTHERAPY

The overall response rate of pre-operative chemotherapy is 75% on average (range 49–100%), whereas fewer than 5% of the patients with operable breast cancer progress during pre-operative chemotherapy and some more do not even show major responses (13). For such patients with progression, the delay of local treatment may be of disadvantage at least in terms of local control. Pre-operative chemotherapy is also associated with significantly increased risk of loco-regional disease recurrence (12).

Another potential disadvantage of pre-operative chemotherapy is the loss of initial histological information such as tumor size, nodal status and biologic markers. According to the current guidelines, application of post-operative chemotherapy is to be decided by weighing the baseline risk, endocrine responsiveness and estimated risk reduction and harm of the treatment (14). Risk of recurrence is estimated based on the clinical and pathological information obtained from surgical specimens. In a pre-operative setting the information on tumor size and nodal status will inevitably be imprecise and intra-tumor heterogeneity of histologic type, histologic grade and biomarker expression cannot be taken into account. It may potentially put patients into danger of over- or under-treatment. Currently, core-needle biopsy is mandatory prior to pre-operative chemotherapy to obtain as much pre-treatment histopathological information as possible.

TREATMENT REGIMENS

Using clinical or pathological responses as surrogate endpoints of overall survival, optimal systemic therapies have been investigated in pre-operative settings in patients with early breast cancer. The general consensus reached is that an anthracycline-containing doublet (doxorubicin or epirubicin with cyclophosphamide) or triplet (doxorubicin or epirubicin with cyclophosphamide and 5-fluourouracil) should be used as the initial chemotherapy strategy for pre-operative chemotherapy (15, 16).

The sequential use of non-cross-resistant agents is likely to augment the response of pre-operative chemotherapy (17, 18), among which taxanes are the most investigated drug. Overall, results of randomized trials indicate that the incorporation of taxane increases the rate of pathological complete response (pCR) by 6–16% compared to anthracycline/cyclophosphamide-based regimens (19, 20). Smith et al. randomized patients who achieved clinical response to the initial four cycles of cyclophosphamide/vincristin/doxorubicin/predonisone (CVAP) therapy to receive further four cycles of CVAP or four cycles of docetaxel (Aberdeen trial) (21). The sequential use of docetaxel resulted in enhanced clinical and pathological responses even in anthracycline-sensitive tumors. In NSABP-B27 trial, the addition of four cycles of docetaxel after pre-operative AC increased the clinical complete response rate (40% versus 63%), clinical overall response rate (86% versus 91%) and the pCR rate (14% versus 26%) compared with pre-operative AC therapy alone (20). However, the addition of taxane in pre-operative or post-operative setting after AC did not improve the long-term outcome in this trial (22).

Treatments incorporating molecular-targeting drugs are of interest. Trastuzumab is effective for patients with advanced...
breast cancer over expressing HER2 (23). In adjuvant settings, at least one year of trastuzumab given sequentially or concomitantly with chemotherapy significantly improves disease-free and overall survival (24, 25). Moreover a short course (9 weeks) of trastuzumab administered concomitantly with docetaxel or vinorelbine seems to be effective in HER2-positive subset of patients in adjuvant settings (26).

For pre-operative settings, there are a limited number of phase II studies reporting the use of trastuzumab (25, 27, 28). The only randomized trial reported was by Buzdar et al., who compared neoadjuvant chemotherapy for HER2-positive, operable breast cancer with or without administration of trastuzumab (29). This study was closed by the recommendation of Data and Safety Monitoring Board of the institution according to early-stopping rule, because pCR rate, the primary endpoint, was strikingly superior in the chemotherapy plus trastuzumab arm (given simultaneously for 24 weeks) compared with the chemotherapy-alone arm (65% versus 26%, \( p = 0.016 \)). We still need to confirm if this significant difference in pathological response will be translated into prolonged overall survival by long-term follow-up and also the cardiac safety of trastuzumab in combination with chemotherapy should be assessed.

CONTROVERSIES OVER PRE-OPERATIVE CHEMOTHERAPY

EVALUATION OF RESIDUAL TUMOR FOR OPTIMAL SURGERY

Optimal imaging modality has not been established to definitively localize the remaining tumor. Usually, serial imaging studies are performed before and after pre-operative chemotherapy. Magnetic resonance imaging or computerized-tomography scanning may supplement conventional breast imaging studies by mammography and ultrasonography (30–33).

The use of functional imaging techniques such as fluorine-18 fluorodeoxyglucose positron emission tomography (\([^{18}\text{F}]\)-FDG PET) is of interest for the evaluation of therapeutic response to systemic therapy in breast cancer. The change in \([^{18}\text{F}]\)-FDG uptake reflects the alteration in cellular glycolysis. Some relatively small studies reported that \([^{18}\text{F}]\)-FDG PET after a single pulse of chemotherapy predicted pCR or minimal residual disease with a sensitivity of 85–100% and a specificity of 74–85% (34–36). FDG-PET is promising for clinical application in future to detect non-responding tumor to avoid unnecessary toxicities from cytotoxic therapy.

FEASIBILITY OF SENTINEL LYMPH-NODE BIOPSY (SNB) IN PATIENTS TREATED WITH PRE-OPERATIVE CHEMOTHERAPY

Axillary staging by SNB may allow omission of axillary dissection in sentinel-node negative patients without compromising the long-term outcome (37). However the optimal timing and feasibility of SNB in the setting of pre-operative chemotherapy have not been established.

Identification rate of SNB following pre-operative chemotherapy are reported to be 84–93% and 78–93%, in single-institution series and multi-center studies (38), respectively. High false-negative rates up to 25–33% have been reported for several small single institution studies (39, 40), but in multi-institutional studies using radiocolloid with or without blue dye, false-negative rates range between 5 and 13% (38), which are similar to those observed when it was carried out before systemic chemotherapy.

There still remain concerns about the use of SNB following chemotherapy in patients with clinically positive axilla (41), SNB after chemotherapy possesses a potential to maximize the benefit of axillary downstaging by pre-operative systemic treatment, in other words, avoidance of complications related to axillary dissection and decision-making of adding further chemotherapy.

ALTERATION OF BIOLOGICAL MARKERS

The changes in the expression of hormone receptors and HER2 protein during pre-operative chemotherapy may influence the clinical decision of adjuvant hormonal and trastuzumab therapy. In studies using immunohistochemistry, the administration of pre-operative chemotherapy did not alter the expression patterns of HER2 and hormone receptors (42–45).

However, a study was conducted to compare gene expression profile of pre-treatment biopsy specimens with those in tumors remaining after doxorubicin-containing pre-operative chemotherapy using DNA array. There were differences in the gene expression profile in tumors that showed a response, but not in tumors that did not respond to therapy (46). Biological and clinical implications of the change of gene expression profile in responding tumors need further elucidation.

DEFINITION OF PATHOLOGICAL RESPONSE

Primary systemic treatment is increasingly recognized as the best model for the quick development of new treatment strategies in early breast cancer. pCR after pre-operative chemotherapy has been chosen as the primary endpoint of clinical trials, because it is validated as the surrogate marker of improved outcome (47, 48). However, diverse definitions of pathological response are used by different investigators (10, 47, 49–53). Some of these grading systems allow inclusion of residual ductal carcinoma in situ (DCIS) without invasive component in the definition of pCR. However, there is no confirmatory data to justify the concept that there is no difference in prognosis between patients with no invasive or in situ disease and those with residual DCIS. Jones et al. investigated whether the prognosis for patients with residual DCIS is the same as that for patients with no residual tumor cells, but could not demonstrate significant
prognostic difference (54). However, this study was statistically underpowered to draw any conclusions.

Ideally, response to chemotherapy should be measured as a continuous variable. No system satisfies the need of accurate pathologic evaluation for the majority of patients who achieve partial or minor response to pre-operative chemotherapy. Rajan et al. proposed that the product of residual tumor size and cellularity might be a more clinically relevant indicator of tumor response than assessing tumor size alone (55). Though it is an interesting proposal, the method needs to be validated in correlation with long-term outcome.

**Outcome after Pre-operative Chemotherapy and Surgery**

Several studies have attempted to find more accurate predictors for survival after pre-operative chemotherapy than pCR in the primary tumor. This is because substantial risk of systemic recurrence still remains even if pCR is achieved, whereas substantial patients have excellent prognosis even if pCR is not achieved. If the long-term risk is high, they will be the candidates for clinical trials to determine whether additional aggressive therapy will be of benefit. If a good prognosis is expected even without good response to pre-operative therapy, aggressive chemotherapy might be overtreatment in pre-operative setting.

In the report of retrospective studies from Royal Marsden Hospital and M. D. Anderson Cancer Center, pathologically negative axillary lymph nodes after pre-operative chemotherapy, not pCR in the primary tumor, remained the independent prognostic factor for disease-free survival and overall survival in multivariate analysis adjusted for other prognostic factors (56–58).

It was revealed by a retrospective multivariate analysis of the clinicopathological factors of the 226 patients who had pCR after pre-operative chemotherapy that pre-operative clinical stage IIIIB, IIIC, and inflammatory breast cancer, axillary lymph nodes more than 10, and pre-menopausal status were the independent prognostic factors of distant metastasis (59). In another study, only histological grading had an independent prognostic impact on disease-free and overall survival after adjustment for pCR to pre-operative chemotherapy containing doxorubicin (60). Carey et al. found that American Joint Committee on Cancer Tumor-Node-Metastasis staging after pre-operative chemotherapy was useful in prediction of distant disease-free survival and overall survival (61).

Rouzier et al. constructed nomograms combining clinical variables associated with pCR that might accurately predict pCR and distant disease-free survival (62). This was confirmed in an independent dataset within the study. The nomogram included size of residual tumor and the number of metastatic nodes at the time of surgery, histologic grade, estrogen receptor (ER) status and histologic type. On the other hand, biologic markers such as expression of HER2 (63), EGFR (64), p53 (65) or MDR1 gene (66) in tumor specimen before pre-operative chemotherapy, reduction of expression in topoisomerase II-α (70) or MLH1 (71) after pre-operative chemotherapy are suggested to predict long-term outcome. Although it is not known whether these markers would add to or replace the nomogram, development of more accurate and comprehensive tools for prediction of prognosis is awaited.

**Prediction of Response to Pre-operative Chemotherapy**

The pre-operative setting is ideal to explore molecular predictors of response to therapy. Various clinical and pathologic variables have been studied. Among them, ER status, histologic grade and smaller tumor size seem to be associated with the response to pre-operative chemotherapy (47, 69).

In previous retrospective studies, clinical and pathological responses to pre-operative chemotherapy appear to be lower in invasive lobular carcinoma (ILC) as compared to invasive ductal carcinoma (IDC), and patients with ILC were more likely to receive mastectomy after initial attempt for breast conservation (70–73). However, low pCR rates in ILC have not been translated into survival disadvantage (70–72). These data suggest that different approach should be taken in the clinical management of patients with ILC.

In a biomarker study, ER expression, absence of HER2 and a decrease in Ki67 correlated with good clinical responses subsequent to a pre-operative chemoendocrine therapy (74). Among other biomarkers, bcl-2 and p53 have been studied. bcl-2 has been shown to protect cells from apoptosis induced by chemotherapeutic drugs (75). Although high expression of bcl-2 has been hypothesized to play a role in resistance to chemotherapy, it is still controversial. In one study, higher bcl-2 expression at diagnosis was predictive of pCR in univariate analysis but it did not retain its impact in multivariate analysis (76), while other studies did not find any correlation between bcl-2 expression and the response (77, 78).

p53 is also a potential predictive marker. Active p53 promotes apoptosis in growth-arrested cells whereas loss of p53 function has been reported to enhance cellular resistance to various chemotherapeutics (79). In a clinical setting, in patients treated with single agent epirubicin, mutant p53 was a significant predictor for poor clinical response, but the association was weaker in patients treated with cyclophosphamide/methotrexate/5FU with or without tamoxifen (65). Another study demonstrated that a tumor expressing wild-type p53 was related to resistance to single agent doxorubicin therapy in multivariate analysis (80). TP53 gene mutation and over expression of p53 were related to epirubicin-containing chemotherapy, but response to paclitaxel seemed to be related to p53-negative tumors (81).

Tumor response and toxicities are different among individual patients. Pharmacogenomic studies aim to elucidate the genetic bases for inter-individual differences and to enable individualization of care. DNA microarray is one of the modern high-throughput biotechnologies that allow
researchers to analyze expression of multiple genes in concert and relate the findings to clinical parameters. In breast cancer, several groups have reported preliminary results suggesting that the gene expression profile of the primary tumor may predict the tumor’s response to pre-operative chemotherapy (82–86). One major limitation of microarray studies is overfitting of the predictor: the number of mRNA transcripts far exceed the number of samples (87, 88). The accuracy of the predictive model is low in independent data set (89). More rigorous and critical evidence is necessary before multi-gene predictors can be accepted as a useful and reliable tool in clinical practice.

PRE-OPERATIVE ENDOCRINE THERAPY

The relative benefit of chemotherapy is less in endocrine-responsive disease as compared with endocrine non-responsive disease (1) and recent consensus of the clinical community lays emphasis on the endocrine responsiveness in decision-making of adjuvant systemic therapy (14). Pre-operative endocrine therapy is an attractive alternative for endocrine-responsive disease, because it is easy to perform and can also avoid acute and late side effects caused by cytotoxic chemotherapy, but pre-operative endocrine therapy has not been accepted as the standard therapy because of the slow rate of response (90). We need more accurate measures to select the patients who are most likely to respond to endocrine therapy without compromising the potential benefit of chemotherapy.

APPLICATION TO MOLECULAR-TARGETED THERAPY

Molecular-targeted drugs are anticipated to individualize the therapeutic strategy based on the biology of the tumor. To date, the presence of a target still does not satisfactorily guarantee a response to therapy, but efforts are being made to elucidate the key components of the molecular pathways targeted by a specific agent.

Moshin et al. reported a pre-operative study of trastuzumab as a single agent in HER2-positive locally advanced breast cancer (91). They administered trastuzumab as a single agent for the first 3 weeks, followed by a combination of trastuzumab and docetaxel. Of note, partial response was observed in eight among 35 patients after only 3 weeks of treatment and can also avoid acute and late side effects of docetaxel was beneficial in terms of disease-free survival not in complete responders or non-responders but only in partial responders in a subset analysis according to clinical response after AC. Who needs additional systemic therapy? Who can avoid systemic therapy?

Development of endocrine therapy and trastuzumab has opened the door to important therapeutic advance of ‘molecular-targeted therapy’. Transcriptional profiling has revealed that expression levels of these targets, i.e. ER and HER2, are the major genetic determinants of the biology of the disease (93). Thus, we can foresee the future of systemic therapy individualized with endocrine responsiveness and involvement of HER2 signaling pathway. However, to date, the predictive value of screening test for molecular targets remains unsatisfactory.

Identification of clinically useful, prognostic and predictive molecular markers is highly anticipated to optimize therapeutic regimens. The current probability-based therapeutic strategy, ‘empiric treatment’ so to speak, might give way to biology-based, individualized strategy, ‘marker-based treatment’, when additional biologic markers are identified that make ‘targeted therapy’ more targeted and effective. Pharmacogenomic researches that accompany pre-operative therapy might help better understand the biology of breast cancer and thus promote the development of new therapeutic strategies.

FUTURE DIRECTIONS

Pre-operative chemotherapy has become the standard of care in management of primary breast cancer. However, we should be aware that a substantial portion of patients may be over-treated by pre-operative chemotherapy because of inaccurate pre-treatment staging. In NSABP-B27 study, addition of docetaxel was beneficial in terms of disease-free survival not in complete responders or non-responders but only in partial responders in a subset analysis according to clinical response after AC. Who needs additional systemic therapy? Who can avoid systemic therapy?

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Conflict of interest statement

None declared.

References

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