Neoadjuvant Chemotherapy in Operable Breast Cancer: The Pros

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The rationale for evaluating preoperative or neoadjuvant chemotherapy in patients with operable breast cancer originated from experimental and clinical observations as well as theoretical hypotheses on tumor cell growth and dissemination [1–7]. Further clinical justification for the use of neoadjuvant chemotherapy in this setting was provided by the demonstration of equivalent survival between breast conserving surgery and mastectomy in patients with early breast cancer [8–12] and by the demonstration of significant improvements in outcome with adjuvant chemotherapy not only in patients with positive nodes but also in those with negative nodes [13, 14]. Based on these developments, neoadjuvant chemotherapy could be employed irrespective of nodal status with the intent to convert patients needing mastectomy to candidates for breast-conserving surgery.

Initial non-randomized studies of neoadjuvant chemotherapy demonstrated high rates of clinical tumor response, low rates of pathologic complete response (pCR) and increase in the rates of breast-conserving surgery [15–21]. However, non-randomized studies could not address the relative efficacy of neoadjuvant vs. adjuvant chemotherapy on disease-free and overall survival. Similarly, early randomized trials [22–26] were not designed as straightforward comparisons of neoadjuvant vs. adjuvant chemotherapy. As a result, those trials could also not adequately address the relative efficacy of each approach on outcome. This question was eventually addressed in large randomized trials that directly compared the two approaches (either with an anthracycline-based regimen or with an anthracycline-taxane-based regimen) [27–31]. These trials demonstrated no significant differences in outcome with neoadjuvant vs. adjuvant chemotherapy and, in addition, confirmed observations from previous studies i.e. that neoadjuvant chemotherapy significantly increased the rate of breast conserving surgery over mastectomy and that there was a significant correlation between achievement of pCR in the breast

and axillary nodes and improved long-term outcome. Based on these results, neoadjuvant chemotherapy became a reasonable alternative to adjuvant chemotherapy in patients with operable breast cancer with several potential advantages over the adjuvant approach.

As mentioned above, the potential for increasing the rates of breast-conserving surgery in patients with operable breast cancer is probably the most important clinical advantage of neoadjuvant vs. adjuvant chemotherapy. It is reassuring that the increase in rate of breast conserving surgery has been achieved without a significant increase in the rate of ipsilateral breast tumor recurrence. Although it was hypothesized that the development of more effective chemotherapeutic regimens (with the incorporation of taxanes) will further increase the rates of breast conserving surgery, this hypothesis was not supported by recently reported results from a large NSABP randomized trial evaluating taxane-based chemotherapy [32]. However, besides converting patients from mastectomy to breast conserving surgery, the use of neoadjuvant chemotherapy has the potential to improve the cosmetic result by decreasing the amount of breast tissue that needs to be removed at the time of lumpectomy. This endpoint, however, is subjective and difficult to quantify and requires an accurate assessment of the patterns of primary tumor shrinkage and the amount of residual disease in the breast following neoadjuvant chemotherapy.

Besides its effects on the primary breast tumor, neoadjuvant chemotherapy has also been shown to downstage axillary lymph nodes in a significant proportion of patients (around 20–30% with anthracycline-containing regimens [27, 30] and close to 40% when a taxane is added [32, 33]). Although this observation was of little clinical significance when axillary node dissection was the sole method for staging the axilla, the development and validation of sentinel node biopsy provided yet another potential advantage for the use of neoadjuvant vs.

adjuvant chemotherapy. Thus, in patients with involved axillary nodes at presentation, down-staging of the nodes with neoadjuvant chemotherapy and performance of sentinel node biopsy instead of axillary dissection could lead to a significant decrease in the extent and morbidity of axillary surgery. This approach is, naturally, predicated on the premise that sentinel node biopsy is feasible and accurate following neoadjuvant chemotherapy. Until recently, only small, single-institution studies have examined the efficacy of lymphatic mapping and the accuracy of sentinel node biopsy after neoadjuvant chemotherapy [34–46]. Because of the small number of patients (and, more importantly, small number of node positive patients) in those studies, significant variability was observed in the rate of sentinel node identification and, more importantly, in the rate of false negative sentinel nodes. However, when these studies are examined collectively or when larger, multi-center data sets are analyzed [47, 48], sentinel node biopsy after neoadjuvant chemotherapy appears to have similar performance characteristics to those of sentinel node biopsy before systemic therapy [49–52].

Following neoadjuvant chemotherapy, the resulting separation of patients into different outcome groups according to the achievement or not achievement of pathologic complete response may provide a significant clinical advantage in patient management. Since this association appears to be maintained with the use of more effective chemotherapy regimens [31, 53, 54], pCR can be used as an intermediate endpoint in determining the value of new chemotherapy regimens or new drugs administered after well-established regimens [55]. From a research standpoint, because this intermediate endpoint can be achieved within weeks from the start of neoadjuvant chemotherapy, the relative efficacy of new regimens can be evaluated promptly and useful information can be obtained without a long waiting follow up period, as is currently the case with the use of adjuvant chemotherapy. From a clinical practice standpoint, by evaluating clinical response to neoadjuvant chemotherapy (a surrogate to pCR) individual patients might be spared from repeated administration of ineffective regimens if these do not translate into prompt tumor response. In the opposite end, one of the original premises for the use of neoadjuvant chemotherapy was that clinical breast tumor response could be used as an *in vivo* chemosensitivity assay in order to predict which patients would or would not benefit from additional (potentially non-cross-resistant) chemotherapy.

Although the existing information on the subject is limited, the preliminary conclusions seem to be somewhat counterintuitive to the original hypothesis, i.e. that patients who do not respond to the initial neoadjuvant chemotherapy regimen might derive the most benefit from subsequent non-cross resistant chemotherapy. In fact, the results so far point to the opposite conclusion – that patients who show a clinical response to the first chemotherapy regimen are those who derive the most benefit from non-cross resistant chemotherapy [53, 56, 57] and those who do not show a clinical response to the first regimen have relatively chemo-resistant disease and derive little, if any, benefit from non-cross resistant regimens [53, 58].

Finally, another advantage of neoadjuvant chemotherapy is the potential for evaluation of many of the proven, as well as putative, prognostic tumor markers and their correlation with clinical and pathologic tumor response and eventually outcome [55]. Furthermore, by serially monitoring biomarker changes during and after neoadjuvant chemotherapy, one could gain biologic insight into the nature and function of these biomarkers (as they relate to chemosensitivity or chemoresistance) and into the mechanism(s) of action of novel chemotherapeutic regimens or new treatment modalities. As we rapidly enter the era of gene expression profiling through the use of high-throughput technology and other novel molecular techniques, clinical and, more importantly, pathologic response to neoadjuvant chemotherapy are useful endpoints for identifying gene profiles that predict for response to a certain chemotherapy agent or particular drug combination [59–63]. This approach has the potential to rapidly optimize the selection of appropriate candidates for particular neoadjuvant therapy regimens avoiding unnecessary toxicity in patients who are unlikely to benefit. Although such an approach can be also utilized in the adjuvant setting, the neoadjuvant setting can provide the necessary information in a much more expeditious fashion allowing us to quickly improve our understanding of tumor biology and individualize treatment options for our patients.

In summary, several advantages exist with the use of neoadjuvant chemotherapy in patients with operable breast cancer. These advantages have significant clinical and biologic implications and will allow us to rapidly evolve our understanding of the disease and to continue to expand the available treatment options for our patients.

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Erratum

In the article

Peripheral Neuroectodermal Tumor (PNET) of the Breast – A 6-Year Follow-Up

(*Breast Care* 2006;1:324–327, printed issue) one author was accidentally left out.

The full author list must read:

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We apologize for this mistake.