Primary chemotherapy: A better overall therapeutic option for patients with breast cancer

More than a century ago, William Halsted synthesized the surgical concepts that culminated in his description of the radical mastectomy. This doctrine was based on the conviction that breast cancer was a locoregional disease, and therefore, a radical surgical procedure with wide tumor-free margins could lead to eradication of all cancer cells and cure breast cancer. However, locoregional therapy alone has proved to be inadequate in curing many patients with early breast cancer. The high propensity of early breast cancer to generate distant micro metastases was recognized in the early 1970s. Based on these theoretical considerations, adjuvant systemic chemotherapy and or hormonotherapy was initially introduced in the treatment of patients with high risk (stage II–IIIA) breast cancer, and more recently, in patients with stage I breast cancer. The long-term value of systemic adjuvant therapy in patients with breast cancer is clearly established [1, 2].

Simultaneously with the development of postoperative adjuvant systemic therapy, primary (also called neo-adjuvant, induction or preoperative) chemotherapy was introduced in the management of patients with locally advanced breast cancer (LABC) [3–6]. Primary chemotherapy represents the use of cytotoxic agents as the first treatment modality, even before definitive locoregional therapy is considered. Our group and the group from the Istituto Nazionale Tumori from Milan pioneered multidisciplinary therapy, including primary chemotherapy with anthracycline-containing regimens followed by locoregional therapy and adjuvant systemic treatments. We enrolled more than 800 patients in five studies over the past 25 years. After primary chemotherapy, 15%–20% and 60%–80% of patients with LABC achieved clinical complete remission and partial remission, respectively. The median survival (OS) for stage IIIA disease has not been reached, and for stage IIIB, it was 37 months. The 10-year OS rates for stage IIIA and stage IIIB was 56% and 26%, respectively [4]. Compared with our historical institutional experience, the local control rate and five- and 10-year DFS and OS rates for LABC were substantially improved by this multidisciplinary program. Breast-conserving surgery was feasible in selected patients with LABC after neo-adjuvant chemotherapy [7].

After neoadjuvant chemotherapy became the standard of care for patients with LABC, primary chemotherapy was introduced in the management of patients with earlier stages of breast cancer. This change in focus was based on preclinical studies and the extensive clinical experience gained in patients with preclinical studies LABC [4, 6, 8–11]. Fisher et al. demonstrated in preclinical studies that removal of a primary tumor increased the growth rate of remaining metastatic deposits [10, 11]. This effect was attributed to a serum growth factor, and was abrogated by pretreatment with cyclophosphamide or tamoxifen. The introduction of systemic therapy at the earliest possible moment after diagnosis was also shown to yield better results than delayed initiation of treatment. There were also potential clinical advantages: one of them was the opportunity to assess the efficacy of systemic therapy in vivo. If no response to systemic treatment is observed, the ineffective regimen could be discontinued to avoid unnecessary toxicity, and institute an alternative (and perhaps more effective) form of systemic therapy. This feature assumes that the primary tumor might serve as a surrogate marker for the behavior of micro metastases, an assumption repeatedly suggested by the close correlation of response to primary chemotherapy and long-term disease-free and overall survival. This was in stark contrast with postoperative adjuvant systemic therapy, a 'blind' treatment, since all detectable evidence of disease has been removed, leaving no possibility to monitor the efficacy of the intervention. Another potential clinical advantage of primary systemic therapy is the reduction in tumor volume (downstaging) and therefore the opportunity to employ less radical forms of locoregional therapy.

Several phase II studies demonstrated the feasibility of this therapeutic approach in patients with early breast cancer [3, 6]. These studies confirmed the high objective response rate to primary chemotherapy and an increase in breast conservation rates compared to historical controls. Based on these clinical observations, several randomized studies were designed. The main objective of the initial randomized phase III trials of primary chemotherapy compared with adjuvant therapy was to demonstrate an improvement in disease-free and overall survival of patients with high risk early breast cancer. A second major objective was to expand the utilization of breast-conserving surgery.

Several potential problems related to the use of primary chemotherapy in patients with early breast cancer were recently reviewed [12]. There is concern related to the perceived lack of preoperative prognostic factor information. For instance, precise knowledge of pretreatment pathological nodal status is unavailable. However, we and others [13–15] demonstrated that residual
tumor size and axillary node status after primary chemotherapy continue to be important prognostic indicators. Another potential problem is the possibility of overtreating patients. In many instances the diagnosis of breast cancer is made by fine-needle aspiration; however, this technique is not able to differentiate between carcinoma in situ and invasive carcinoma. This may lead to overtreatment of a small number of patients who have only carcinoma in situ. Therefore, patients should not receive primary chemotherapy until invasive cancer has been clearly documented. The optimal surgical treatment of patients with early breast cancer raises several issues after primary chemotherapy. These include the type and extent of the surgical procedure, margins, and the selection of candidates for breast conservation surgery [7, 12].

In this issue, Makris et al. present the final results of a randomized clinical trial that compares the results of primary and adjuvant chemotherapy in operable breast cancer [16]. This report confirmed the initial results presented by the authors in 1995 [17]. In this trial, 309 patients with operable breast cancer were randomized to receive postoperative adjuvant chemoendocrine therapy or primary systemic therapy with the same regimen (mitoxantrone, methotrexate, +/- mitomycin and tamoxifen). The overall objective response rate, clinical complete response rate and pathological response rate after primary chemoendocrine therapy were 83%, 22% and 10%, respectively. Ten percent had only residual ductal carcinoma in situ. These results are similar to those reported by other investigators in phase II—III trials with primary chemotherapy [3, 4, 6, 18—22]. The disease-free survival (DFS) and overall survival (OS) rates were 77% and 84% for the adjuvant group, and 80% and 86% for the primary chemoendocrine group. The results from this trial and from the largest reported randomized controlled study (B-18) performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) [16, 17] failed to demonstrate an improvement in disease-free (DFS) and overall survival (OS) in patients with operable breast cancer. However, primary chemotherapy was as effective as adjuvant chemotherapy in both studies. In fact, in all reported controlled trials DFS and OS were at least equivalent, and in a few instances slightly better after primary chemotherapy than after postoperative adjuvant systemic therapy. On the other hand, in both the Makris and NSABP B-18 trials the second objective was met. Primary chemotherapy produced downstaging in both the primary tumor and axillary lymph node involvement, reducing the requirement for modified radical mastectomy and enhancing the use of breast-sparing procedures. In the Makris study, a mastectomy was performed in 22% and 10% of patients in the adjuvant and primary groups, respectively. In B-18, 60% in the adjuvant chemotherapy group and 68% in the primary chemotherapy group had a breast-sparing procedure.

Over the past 20 years, the indications for adjuvant systemic therapy have expanded substantially. Today, patients in all age groups who present with lymph node-positive breast cancer, and most patients with lymph node-negative breast cancer (perhaps excluding T1a and T1b tumors) are advised to receive adjuvant systemic therapy as part of optimal multidisciplinary management of primary breast cancer. Furthermore, a number of recent clinical trials have indicated that the combination of chemotherapy and hormone therapy produces better results than either therapy alone, in both node-positive and node-negative patient groups. Based on these considerations, and perhaps with the exclusion of T1a and T1b primary breast cancers, primary chemotherapy would be the strategy of choice once the presence of invasive breast cancer has been clearly established. There is one additional aspect in favor of primary versus postoperative administration of systemic therapy. The administration of primary chemotherapy (or hormone therapy) before the removal of the tumor also provides the opportunity to sample tumor tissue during treatment, and to observe the effects of therapy on a variety of biological endpoints. Chemotherapy reduces the incidence of aneuploidy, and is associated with lower growth rate, as measured by S-phase fraction, or other markers of cell proliferation. Perhaps modifications in other discrete molecular markers are also associated with long-term outcome.

Several therapeutic strategies are under evaluation to improve the results of treatment in patients with high risk primary breast cancer. In experimental systems, there is a steep dose-response curve for most chemotherapeutic agents. Although the dose-response curve may be linear for cytokinetically homogenous experimental tumors, it deviates from linearity as a result of tumor heterogeneity. The steepness of the dose response curve is related to the sensitivity of the tumor to a given drug. Moderate dose intensification of standard agents such doxorubicin and cyclophosphamide, or high-dose combination alkylator chemotherapy with hematopoietic support, are two major areas under clinical investigation. Results of recently reported randomized clinical trials with anthracycline-containing adjuvant chemotherapy regimens demonstrated that dose reduction below standard dose was associated with inferior DFS and OS rates [23, 24]. On the other hand, increasing doses above the standard dose of anthracycline failed to show any additional benefit from the higher doses [25, 26]. Also, reports from two randomized studies that evaluated a range of doses of cyclophosphamide failed to show any additional benefit from higher doses [27]. While higher than standard doses did not improve the outcome of these patients, the high-dose arms were associated significantly with higher hematological and non-hematological toxicities. The role of bone marrow ablative doses of chemotherapy with peripheral hematopoietic stem-cell support is currently under evaluation in several large, randomized clinical trials. The role of this strategy is also being determined after primary chemotherapy as a consolidation chemotherapy. Two recently reported small studies showed similar four-year DFS and OS rates for the two groups [28, 29].
Another strategy to improve the outcome of patients with high risk early breast cancer is the introduction of new chemotherapeutic agents. The taxanes, paclitaxel and docetaxel, are novel antimitotubule agents that bind reversibly and specifically to the β-subunit of tubulin. Paclitaxel has significant anti-tumor activity efficacy against MBC, even in patients with anthracycline-resistant tumors [30, 31]. Henderson et al. reported the preliminary results of a phase III trial of adjuvant doxorubicin/cyclophosphamide (AC) or the same treatment followed by four additional cycles of paclitaxel: there was a statistically significant improvement in both DFS and OS in favor of the paclitaxel group [25]. We recently completed a randomized clinical trial of primary chemotherapy in patients with stage II and IIIA breast cancer, comparing single-agent paclitaxel with standard FAC. The preliminary results demonstrated a similar objective response rates, frequency of downstaging, and breast conservation rate [32]. Very encouraging results were also reported in a phase II trial of single-agent high-dose weekly paclitaxel in patients with LABC [33]. Docetaxel is a semisynthetic compound that also demonstrated significant activity and has shown incomplete cross-resistance with anthracyclines and paclitaxel [30, 34, 35]. The preliminary results of the first neoadjuvant study were recently presented [36]. Patients with LABC received four cycles of docetaxel, followed by surgery, and by four cycles of standard-dose AC. The clinical objective response rate was 83%. A major study phase III trial currently being conducted by NSABP (B-27) randomly assigned patients with operable breast cancer to four cycles of doxorubicin and cyclophosphamide, or the same chemotherapy followed by four cycles of docetaxel either prior to or after surgery. Vinorelbine is a semisynthetic vinca alkaloid that differs from the other members of the vinca alkaloid family by a substitution on the catharanthine ring of the molecule instead of the vindoline nucleus. The efficacy of vinorelbine has been extensively studied in several phase II–III trials in women with metastatic breast cancer [37]. The role of vinorelbine in combination, in patients with early and LABC is currently being determined in several studies. Primary chemotherapy with vinorelbine, methotrexate and epirubicin produced a response rate of 77% (pathological complete response 21%) and allowed breast preservation in 83% of patients. In a second primary chemotherapy trial the combination of vinorelbine, THP-doxorubicin and cyclophosphamide demonstrated a response rate of 92%, including a 23% pathological complete response rate [37].

In summary, primary chemotherapy/hormonotherapy has a potentially better therapeutic index than adjuvant chemotherapy. It provides locoregional control, long-term disease-free and overall survival rates similar to those of adjuvant therapy. In addition, primary chemotherapy/hormonotherapy also provides several major therapeutic advantages. One advantage is the possibility of assessing in vivo response to specific chemotherapy agents or regimens. Moreover, the down-staging effect improves the possibility of breast-conserving surgery and cosmesis in women with early breast cancer. At the present time, primary chemotherapy/hormonotherapy followed by locoregional treatment is the standard of care for patients with stage IIIb breast cancer. However, given the results of Makris’ and other studies [17–21], primary chemotherapy should become the treatment of choice for patients with stage II–IIIa breast cancer and in selected patients with stage I. Several issues remain unsolved at this time. We need to develop better biological markers to be more selective in our therapeutic approach. The role of preoperative hormone therapy has not been defined; therefore, clinical trials designed to establish the value of adding hormonal therapy prior to, concurrent with or after chemotherapy are necessary [38]. After primary chemotherapy, it is unclear what the optimal sequence of subsequent therapies should be, whether one or two local treatment modalities are necessary, or if additional or different postoperative chemotherapy is also needed. Additional refinements of these strategies, including the selection of postoperative chemotherapy based on the response to induction chemotherapy, may further improve the outcome in this group of patients. The role of sentinel node mapping is being evaluated as a tool to assess the effects of primary chemotherapy. Clinical trials to determine the role of new and effective cytotoxic agents, such as docetaxel, paclitaxel, and vinorelbine, are ongoing. Our increasing understanding of cancer molecular biology has led to the identification of new and unique targets for treatment. Monoclonal antibodies to specific tumor antigens, oncogenes, growth factors, or their receptors, and agents affecting tumor angiogenesis and apoptosis have opened the possibility of innovative and potentially more selective therapeutic strategies in the management of patients with early breast cancer.

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