Neoadjuvant Systemic Therapy: Promising Experimental Model or Improved Standard of Care?

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Neoadjuvant therapy (preoperative and primary systemic chemotherapy) was originally developed to improve management of patients with locally advanced breast cancer (LABC), in the hope that it would render inoperable disease operable. In 1988 results from the first longitudinal series of stage III breast cancer patients treated with this approach were published by Gabriel N. Hortobagyi, MD, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, and colleagues. In this study, neoadjuvant chemotherapy (NACT) followed by surgery, radiotherapy, and further adjuvant chemotherapy resulted in 5-year disease-free survival (DFS) rates of 84% and 33% for stage IIIa and IIIb patients, respectively [Hortobagyi GN et al. *Cancer* 1988]. Importantly, this landmark study also suggested that tumor response to NACT correlated well with patients' overall survival (OS). Dr. Hortobagyi discussed the development of neoadjuvant therapy for patients with breast cancer, summarizing past experiences and reviewing its current use as a therapeutic research tool.

The Rational for Neoadjuvant Therapy

The primary rationale for developing neoadjuvant systemic therapy was to convert inoperable LABCs into operable cases by reducing disease burden. Neoadjuvant therapy also has the potential to allow tumors only amenable to mastectomy to become potential candidates for breast-conserving surgery. Beyond these surgical benefits neoadjuvant therapy allows for the earlier initiation of systemic therapy than conventional adjuvant treatment does, and permits a real-time *in vivo* assessment of a therapy's antitumor effect and the opportunity to assess surrogate biologic endpoints. A potential disadvantage of the neoadjuvant approach is that systemic therapy decisions are made on the basis of a core needle biopsy, which may not reflect tumor heterogeneity. Furthermore, the ideal approach to staging of the axilla (ie, sentinel node biopsy before chemotherapy) remains an issue of controversy.

Early preclinical and clinical studies provided support for the development of neoadjuvant therapeutic approaches. A study of mice bearing mammary carcinomas suggested that the most effective control of metastases is achieved when the largest tolerable dose of chemotherapy is given at the time of or before primary tumor removal [Fisher B et al. *Cancer Research* 1983]. In addition, an early prospective randomized trial of neoadjuvant versus adjuvant therapy in patients with LABC suggested the neoadjuvant approach has an advantage for OS (n=414; 86% vs 78%; p<0.04) [Scholl SM et al. *Eur J Cancer* 1994].

The efficacy of neoadjuvant versus adjuvant chemotherapy has since been more formally assessed in a large number of randomized controlled trials. A Cochrane review of 14 studies that randomized a total of 5500 women with operable breast cancer found that neoadjuvant therapy versus adjuvant therapy resulted in equivalent DFS (HR, 0.97; 95% CI, 0.89 to 1.07; p=0.58), increased breast conservation rates (risk ratio [RR], 0.71; 95% CI, 0.67

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to 0.75; p<0.00001), and an increase in the local-regional recurrence rate (RR, 1.34; 95% CI, 0.85 to 2.13; p=0.21) but not in patients treated with surgery (HR, 1.12; 95% CI, 0.92 to 1.37; p=0.25) [van der Hage JH et al. *The Cochrane Library* 2009].

Pathologic Complete Response as a Predictor of Outcome

Analysis of DFS and OS in NSABP B-18, one of the landmark trials of adjuvant versus neoadjuvant therapy, showed that neoadjuvant therapy was equivalent to adjuvant therapy and patients who achieve a pathologic complete response (pCR) to neoadjuvant treatment demonstrated superior DFS and OS [Rastogi P et al. *J Clin Oncol* 2008]. Most pCRs have been observed in patients with estrogen receptor (ER)-negative, high-grade, and highly proliferative tumors. In the Cochrane review, achievement of pCR was associated with improved OS (HR, 0.48; 95% CI, 0.33 to 0.69; p<0.0001) and DFS (HR, 0.48; 95% CI, 0.37 to 0.63; p<0.00001) [van der Hage JH et al. *The Cochrane Library* 2009]. According to Mehta [*J Clin Oncol* 2008], each 10% increment in pCR translates into an absolute 2.6% improvement in 3-year survival.

Response-Guided Treatment Selection

A wide variety of tools tools have been investigated as a way to assess the effects of neoadjuvant therapy, including assessment of clinical response, pCR, residual tumor burden, TNM stage after therapy, post-therapy tumor Ki67 staining scores, and imaging modalities (ultrasound, MRI, and positron emission tomography scans). Novel tools based on serial biopsies, such as the preoperative endocrine prognostic index, are also being validated as potential techniques to make early inferences about an individual patient's response to treatment and, hence, direct therapy in real time. Clinical and pathologic factors that predict for pCR include high tumor grade, ER-negativity, human epidermal growth factor 2 (HER2)-positivity, tumor subtype (higher rates in triple-negative tumors), high tumor cell proliferation makers, and a rapid onset of clinical response. There is no individual pathologic or molecular marker that can reliably predict response to neoadjuvant therapy in individual patients. However, Rouzier et al. [*J Clin Oncol* 2005] reported that a multivariable nomogram based on clinical stage, ER status, histologic grade, and number of preoperative chemotherapy cycles accurately predicted pCR after neoadjuvant therapy for breast cancer.

Another clinical question is, "Can an early assessment of tumor response to neoadjuvant chemotherapy be used to guide subsequent treatment, on the basis that a lack of response to initial therapy might warrant a change in systemic treatment?" Two trials have addressed this issue. In the first, tumor response to neoadjuvant therapy was assessed at surgery and used to guide subsequent adjuvant treatment. Patients demonstrating a good response to initial therapy were continued on further cycles of the same therapy, but those with a poor response were randomized to continuing the same or switching to an alternate non-cross-resistant regimen [Thomas E et al. *J Clin Oncol* 2004]. Those randomized to a switch showed a trend towards improved DFS and OS. In the second study, the GeparTrio trial, interim response-guided NACT versus conventional therapy improved DFS (HR, 0.71; 95% CI, 0.60 to 0.85; log-rank p<0.001) [von Minckwitz G et al. SABCS 2011]. This benefit was seen primarily in patients with luminal A and luminal B, HER2-negative tumors.

According to Dr. Hortobagyi, primary systemic therapy is optimal for all patients who are candidates for systemic therapy. He emphasized that primary systemic therapy should be tailored to the biological profile of the primary tumor. Primary systemic therapy is not indicated when systemic therapy is not indicated, primary or lymph node metastases cannot be measured and monitored, the patient is not compliant, or a multidisciplinary team is not available.

NACT for operable primary breast cancer downstages the primary tumor and axillary lymph node involvement and increases the breast conservation rate. It can affect local control in the absence of optimal multidisciplinary planning, and it may affect survival. Dr. Hortobagyi concluded that NACT is the treatment of choice for LABC and inoperable breast cancer, and an acceptable and preferred alternative to surgery followed by adjuvant chemotherapy for most patients with T2 and T3 breast cancer. NACT is also an excellent translational research tool. Future applications of NACT include definitive treatment without surgery, new drug development, monitoring biological endpoints, and randomized neoadjuvant therapy trials to justify or avoid randomized adjuvant therapy trials.