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Review

Current approaches for neoadjuvant chemotherapy in breast cancer

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ABSTRACT

Compared to adjuvant chemotherapy, the administration of the same regimen in the neoadjuvant setting provides women with identical improvements in disease free and overall survival. Neoadjuvant chemotherapy may offer benefits to properly selected women such as broadening surgical options and enhancing the likelihood of breast conservation. Assessment of response to neoadjuvant chemotherapy provides women with an individualized estimate of prognosis. For example, a woman who achieves a complete pathological response following neoadjuvant chemotherapy has a very low risk of recurrence compared to a woman with similar tumor characteristics and a large residual disease. In this review we will provide a historical perspective and discuss the aims of neoadjuvant chemotherapy in primary operable breast cancer; as well as appropriate patient selection, treatment strategies, response monitoring, and postoperative care. We will also discuss the attractiveness of this approach to study the mechanism of action of standard and novel agents, and the role of predictive biomarkers of response to treatment and outcomes.

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1. Introduction

Breast cancer-related outcomes have improved in Western societies in recent decades. These improvements are attributed in part to early detection through screening and to more optimal local and adjuvant systemic therapies (Berry et al., 2005). The majority of women with early breast cancer will be offered both local and systemic therapies to reduce the risk of recurrence and death. The types and extent of treatment are recommended based on the tumor stage and characteristics such as grade, expression of estrogen (ER) and progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) status. Traditionally, most women undergo a definitive surgical procedure,

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which allows for accurate staging, prediction of survival outcomes, and systemic treatment recommendations. Few women present with locally advanced, unresectable disease and require the administration of systemic treatment prior to local therapy. In these women, the administration of neoadjuvant chemotherapy, also designated primary or preoperative chemotherapy, is often associated with a reduction in tumor volume that facilitates definitive local therapy.

The success observed in the locally advanced setting, the wide implementation of adjuvant chemotherapy, as well as data from preclinical models has led to investigations of neoadjuvant chemotherapy in women with resectable yet large primary tumors. In aggregate, multiple randomized clinical trials have demonstrated that neoadjuvant chemotherapy is associated with identical disease-free and overall survival compared to the administration of the same therapy in the adjuvant setting (Mauri et al., 2005). Neoadjuvant chemotherapy may provide individual women with additional benefits such as improvement of surgical options and enhancement of breast conservation. The approach has also become an attractive model for new drug investigation and for studies of predictive biomarkers of treatment response and outcome. In this review, we will discuss the aims and advantages and disadvantages of neoadjuvant chemotherapy, appropriate patient selection, the necessity for multi-disciplinary care, current and investigational treatment strategies, response monitoring, and the promise this approach holds in new drug investigation.

2. Historical perspectives and aims of neoadjuvant chemotherapy

Historically, women diagnosed with breast cancer were first recommended local therapy, with emphasis on surgical removal of breast tissue and loco-regional lymph nodes. Subsequently, results of multiple randomized clinical trials have demonstrated unequivocally that adjuvant chemotherapy improves disease-free and overall survival (Peto et al., 2012). Adjuvant chemotherapy is commonly recommended to women with stage 2 or 3 breast cancer and to those with high risk stage 1 disease (Carlson et al., 2009). Given the improvements in survival outcomes observed with adjuvant chemotherapy, investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) led by Dr. Bernard Fisher hypothesized that, compared to adjuvant chemotherapy, the administration of the same regimen in the neoadjuvant setting would improve survival outcomes by early elimination of micrometastatic systemic disease. Indeed, the hypothesis was supported by early animal studies demonstrating superior outcomes in mice receiving systemic therapy prior to surgical removal of a tumor (Fisher et al., 1989).

One of the initial clinical trials testing the hypothesis, designated NSABP Trial B-18, was designed to determine whether the neoadjuvant combination of four cycles of doxorubicin and cyclophosphamide (AC) would more effectively prolong disease-free and overall survival than the same chemotherapy given in the adjuvant setting. Another objective was to determine if the neoadjuvant chemotherapy would permit a more conservative breast surgery and reduce the incidence of ipsilateral breast tumor recurrence by minimizing the tumor size (Fisher et al., 1997). Survival outcomes were identical among the two groups, with hazard ratio (HR) 0.93 (95% confidence interval [CI], 0.81–1.06; $P=0.27$) for disease-free survival and 0.99 (95% CI, 0.85–1.16; $P=0.90$) for overall survival (Rastogi et al., 2008). Although neoadjuvant chemotherapy did not improve disease-free and overall survival, a higher proportion of women who received neoadjuvant therapy were able to undergo breast conserving surgery compared to the adjuvant group (68% and 60%, respectively, $P=0.001$). Therefore, a main goal of neoadjuvant chemotherapy is to enhance surgical options and breast conservation (Kaufmann et al., 2006, 2007). Dozens of trials have demonstrated similar results and the administration of neoadjuvant chemotherapy has become an attractive approach to women with stage 2 or 3 breast cancer who are not candidates for breast conservation.

Importantly, the response to therapy is a powerful individualized prognostic factor. Women who achieve a pathological complete response in the breast following neoadjuvant chemotherapy are expected to experience excellent disease-free and overall survival compared to women with large residual disease. In B-18, women achieving a pathological complete response in the breast had superior disease-free survival (DFS) and overall survival (OS) compared to those who did not achieve a pathological complete response (DFS HR=0.47, $P=0.0001$; OS HR=0.32, $P=0.0001$) (Rastogi et al., 2008).

Different groups have used varied definitions of pathological complete response which may have indicated the absence of invasive disease in the breast, or both in the breast and lymph nodes (Kuerer et al., 1999; Carey et al., 2005). Others have proposed more continuous definitions such as a residual stage or combination of anatomical and histopathological features (Chevallier et al., 1993; Sinn et al., 1994; Sataloff et al., 1995; Symmans et al., 2007). Regardless, in each of these reports, absence of disease in both the breast and lymph nodes provides the best overall outcome.

Investigations of neoadjuvant chemotherapy over the years have produced additional value by both providing data regarding selection of agents or combinations and the appropriate identification of patient populations most likely to benefit from the approach. Women should be observed closely during treatment and if there is a concern for progressive disease they should be transitioned to an alternative regimen or to a local treatment. Finally, the neoadjuvant treatment approach has become an important vehicle for new drug and biomarker investigation. Response can be assessed clinically or with standard and functional imaging. Moreover, access to tumor tissue is relatively non-invasive and allows both for assessment of biomarker modulation following standard or novel treatment and the study of drug mechanism of action.

Women should be informed that neoadjuvant chemotherapy may be associated with potential disadvantages. Initial studies raised concern that breast conserving surgery was associated with increased locoregional recurrence risk. However, newer studies suggest that with adequate free margins, the risk of locoregional recurrence is not higher in women administered neoadjuvant chemotherapy compared to those receiving the same regimen in the adjuvant setting. Another concern is that the inability to determine an accurate pathological stage may be a disadvantage of neoadjuvant chemotherapy. However, the knowledge of residual disease may provide a more personalized prognostic value.

Since disease-free and overall survival are equivalent when the same regimen is administered in the adjuvant or neoadjuvant setting, discussions with an individual woman should focus on the potential benefits and possible disadvantages she may encounter. Once neoadjuvant chemotherapy is initiated, women should be well informed of the goals of treatment, the required preoperative assessment, monitoring response, local treatment considerations, and post-treatment evaluation.

3. Selection of patients

Members of an International Consensus Expert Panel have suggested that neoadjuvant chemotherapy should be considered in any individual for whom adjuvant chemotherapy is indicated (Kaufmann et al., 2006, 2007). Once a decision has been made to administer chemotherapy, the entire recommended chemotherapy regimen should be ideally delivered prior to the local therapy. Therefore, a