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ORIGINAL PAPER

Preoperative Systemic Chemotherapy and Pathologic Assessment of Response

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Abstract Preoperative systemic (neoadjuvant) chemotherapy is both routine therapeutic modality for locally advanced breast cancer and a translational research model to identify biomarkers that predict treatment response. It is imperative that pathologic response be strongly prognostic in order to optimize the clinical and scientific information that can be gained from neoadjuvant clinical trials. Dichotomization of response as pathologic complete response (pCR) or residual disease (RD) is overly simplistic for these objectives, particularly because residual disease (RD) after neoadjuvant treatment includes a broad range of actual responses from near-pCR to frank resistance. More effective or prolonged neoadjuvant treatments should reduce the extent of RD in many patients, possibly blurring the prognostic distinction between pCR and RD. On the other hand, it should be possible to identify patients with resistant disease in order to develop predictive tests for this adverse outcome. Our research group recently proposed to measure residual cancer burden (RCB) as a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. Each component contributes meaningful pathologic information and can be obtained using routine pathologic materials and methods of interpretation that could easily be implemented in routine diagnostic practice.

Keywords Preoperative systemic therapy · Breast cancer

Preoperative systemic (neoadjuvant) chemotherapy is a routine therapeutic modality for locally advanced breast cancer and is also increasingly used in the treatment of operable breast cancer. The primary benefit from preoperative chemotherapy is reduction in tumor size and conversion of positive lymph nodes into node-negative status. Clinical tumor response is observed in 70–90% of cases depending on the type of chemotherapy and number of courses [1]. Tumor response can render previously inoperable tumors operable, lead to increased breast conservation rate and also results in smaller resection volumes [2, 3]. Despite smaller surgical resection volumes, randomized clinical trials did not demonstrate significantly higher locoregional relapse rates after preoperative chemotherapy compared to surgery first, although some studies suggested a non-significant trend for higher local and regional recurrence [4, 5]. Several randomized clinical trials established that long-term overall- and disease-free survivals are similar after neoadjuvant and adjuvant chemotherapies when the same regimen is used either pre- or post-operatively [6].

However, the administration of preoperative chemotherapy is logistically more complex than the administration of adjuvant chemotherapy. It requires regular monitoring of tumor response because a minority of patients may progress on treatment which requires discontinuation of therapy and prompt referral to surgery or preoperative radiation therapy (if the tumor is inoperable). Unfortunately switching treatment regimens rarely improves pathologic response rates in highly chemotherapy-resistant tumors [7, 8]. Complete clinical and pathologic response to therapy can render localization of the tumor bed difficult for the pathologist therefore it is common practice to place anatomical markings (i.e. metallic beads, skin tattoo) to identify the tumor bed. Complications during chemotherapy can lead to delays in the final surgical treatment. These logistic complexities explain the relatively infrequent use of neoadjuvant chemotherapy in routine management of operable breast cancer. However, it is an increasingly popular treatment strategy in academic centers because it provides unique opportunities for predictive marker research [9].

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It has been argued that preoperative systemic therapy leads to loss of prognostic information, particularly to the loss of ability to establish baseline TNM stage. However, pathologic tumor size and nodal status after preoperative chemotherapy remains as powerful a predictor of long-term survival as baseline TNM stage [10]. Pathologic complete response (CR) has been adopted as the primary endpoint for neoadjuvant chemotherapy trials because of its consistent association with long-term survival. It is generally held that a definition of pCR should include patients without residual invasive carcinoma in the breast (pT0). However, the presence of nodal metastasis, minimal residual invasive cancer, and residual in situ carcinoma are not consistently defined as pCR or residual disease (RD). When there is no residual invasive cancer in the breast, the number of involved axillary lymph nodes is inversely related to survival. Conversely, patients who convert to node-negative status after treatment have excellent survival, even if there is residual disease in the breast [11, 12]. Consequently, inclusion of patients with positive lymph nodes after chemotherapy in the definition of pCR weakens its prognostic value. Some investigators excluded patients with residual ductal carcinoma in situ (DCIS) from the definition of pCR. However, residual DCIS after chemotherapy has no adverse effect on any clinical outcome, therefore exclusion of these patients from the pCR category is not justified and may weaken the statistical power of clinical trials that use pCR as outcome [13]. It is also important to consider that dichotomization of response as pCR or residual disease (RD) is overly simplistic for these objectives, particularly because residual disease (RD) after neoadjuvant treatment includes a broad range of actual responses from near-pCR to frank resistance and disease progression. Our research group recently proposed to measure residual cancer burden (RCB) as a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden (www.mdanderson.org/breastcancer_RCB) [14]. An important novel feature of this measure is that it enables one to define a subset of minimal residual cancer that has the same excellent survival as those with pCR.

In order to decide if neoadjuvant chemotherapy is the most appropriate treatment for an individual, markers that predict probability of response, particularly pCR, would be helpful. Three types of information can be used to estimate the probability of pCR to preoperative chemotherapy. These include, (1) clinical tumor response after two course of treatment, (2) clinical phenotype of the cancer including ER-status, grade and age, and (3) molecular markers. Several trials indicated that the absence of clinical response after the first two to four cycles of chemotherapy predict for low probability of pCR even after four to six courses of further therapy [7, 8]. Switching to a different type of regimen unfortunately also does not seem to alter this poor response [15]. High histologic grade, ER-negative status and younger age are each consistently associated with higher rates of response (including pCR) to chemotherapy. It is possible to combine these clinical variables into a prediction model. One such model, that has been validated on independent data is freely available at the web site: www.mdanderson.org/care_centers/breastcenter/dIndex.cfm?pn=448442B2-3EA5-4BAC-98310076A9553E63 [16]. Among the frequently used molecular markers, HER-2 amplification, high Ki 67% expression (and other proliferation markers) as well as high OncotypeDX recurrence score are associated with higher chemotherapy sensitivity [17, 18].

In summary, preoperative chemotherapy is an appropriate treatment option for most patients for whom adjuvant chemotherapy is indicated. It is the preferred option for locally advanced breast cancer and it also represents an ideal clinical setting for predictive marker research. The amount of residual invasive cancer after therapy is an important prognostic predictor. Additional valuable information on primary systemic chemotherapy can be found at the following web site: http://ctep.cancer.gov/bcmeeting/index.html#agenda.

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