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Neoadjuvant chemotherapy: practice and thinking for Chinese patients with early breast cancer

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Although some researchers hypothesized that neoadjuvant chemotherapy may improve prognosis of patients with breast cancer because it allows them to receive earlier systemic treatment, no large randomized controlled trials have confirmed this hypothesis. Thus, it is generally accepted that there is no difference in disease-free survival (DFS) or overall survival (OS) for patients receiving neoadjuvant or adjuvant chemotherapy for breast cancer.[1,2] Karagiannis *et al*[3] published an article in 2017 that incited some controversy because it reported that neoadjuvant chemotherapy promoted breast cancer micrometastasis to the blood vessels and lungs, based on the study of a polyomavirus middle T antigen mouse model and human xenograft *in vivo* and in fixed tissue.

However, disagreement remains among researchers and practitioners worldwide regarding the advantages and disadvantages of neoadjuvant chemotherapy for breast cancer. There is a consensus, however, regarding some of the major possible benefits of neoadjuvant chemotherapy. In particular, neoadjuvant chemotherapy reduces tumor size in preparation for surgery, improves resection rates for locally advanced breast cancer, and increases the rate of breast-conserving surgery for some larger tumors. For patients with inoperable tumors or locally advanced breast cancers having no chance of breast-conserving surgery, neoadjuvant chemotherapy is a very important option. The widely acknowledged disadvantage of neoadjuvant chemotherapy is that it prolongs the time tumor remains in the body. And for some patients, neoadjuvant chemotherapy delays surgery, increases the local recurrence rate and leads to diagnostic errors secondary to limited tumor biopsy analysis.[2] Furthermore, excessive treatment may be administered to patients with better prognosis so that prognosis and treatment selection data may be biased.

At the former St. Gallen Consensus Conference, 94.1% of professionals preferred neoadjuvant chemotherapy for treatment of stage II/III human epidermal growth factor receptor 2 (HER2)+ breast cancer, and 92.5% preferred neoadjuvant chemotherapy for treatment of stage II/III triple-negative breast cancer (TNBC). The published consensus statement strongly endorsed the use of neoadjuvant therapy for stage II/III breast cancer that was HER2+ or TNBC as the preferred initial treatment, particularly when treatment may lead to de-escalation of subsequent surgery or radiotherapy.[4]

However, we do not fully disagree with this consensus statement, as do some other scientists. Instead, we agree with Vaidya *et al*[5] that neoadjuvant chemotherapy should be used prudently because that many patients might miss the opportunity for surgical tumor removal due to poorly managed neoadjuvant chemotherapy. Different medical providers reported highly variable neoadjuvant chemotherapy practices for Chinese patients with early breast cancer (EBC). Herein, we will discuss our opinions on neoadjuvant chemotherapy.

Pathological complete response (pCR) should not be the ultimate endpoint by which treatment efficacy is evaluated. Although the B-18 and B-27 studies showed that patients who underwent neoadjuvant chemotherapy had better prognoses when they achieved a pCR,[6] these studies also demonstrated that DFS and OS did not differ for those receiving neoadjuvant or adjuvant chemotherapy. The goal of breast cancer treatment is to improve quality of life and prolong survival, but a pCR is a measure of the tumor's response to treatment. Therefore, relapse may occur in patients who do or do not achieve a pCR. For this reason, pCR should not be used as a surrogate end-point for DFS and OS, and should not be pursued as the primary goal of breast cancer treatment, especially for treatment of EBC.

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The diagnosis of an aggressive molecular subtype, such as TNBC and HER2+ breast cancers, by itself, does not justify the use of neoadjuvant chemotherapy, even though most of these breast cancers are associated with a poor prognosis. Because the pCR rate for TNBC and HER2+ breast cancers following neoadjuvant chemotherapy is high,[7] especially in HER2+ breast cancers treated by double targeted therapy (such as reported in the NeoSphere and TRYPHAENA trials), some researchers believe that all patients with these breast cancer subtype should be treated with neoadjuvant chemotherapy.[8,9] However, no prospective studies have yet compared neoadjuvant to adjuvant chemotherapy for TNBC or HER2+ breast cancer. In fact, some studies showed that most patients who did not achieve a pCR following neoadjuvant therapy missed the opportunity for surgery because of rapid tumor progression.[7] The National Comprehensive Cancer Network also recommended considering the possibility of disease progression during preoperative systemic therapy. Thus, although some patients achieve pCR following neoadjuvant chemotherapy, others may experience treatment failure or rapid progression. In fact, TNBC or HER2+ status is only one factor that affects pCR. Advocates of neoadjuvant therapy have commented that non-pCR patients may still benefit from intensive treatment or remedial treatment, as indicated in the CREATE-X and Katherine trials. However, neither of these studies has intensified treatment for pCR patients as well at the same time.

Early use of systemic neoadjuvant chemotherapy does not confer a survival benefit compared to adjuvant chemotherapy, and the time when neoadjuvant and adjuvant chemotherapy begins typically only differ by about 2 weeks. More specifically, at least 1 week is generally required to obtain tissue pathology results following core needle biopsy and adjuvant chemotherapy generally begins 2 weeks after surgery to allow time for recovery and wound healing. However, neoadjuvant chemotherapy usually lasts for several months, and it therefore significantly increases the time during which a tumor can grow or metastasize. Some patients who undergo neoadjuvant chemotherapy may lose the option for surgery and cure.

Another reason for favoring adjuvant over neoadjuvant therapy is that ideal drug sensitivity testing cannot be performed with neoadjuvant chemotherapy, and replacement of tumor-resistant drugs in neoadjuvant chemotherapy regimens does not confer a survival benefit. In contrast to adjuvant chemotherapy, neoadjuvant chemotherapy is administered in the presence of a tumor, thereby allowing direct observations needed for *in vivo* drug sensitivity testing. Because of this, many researchers prefer neoadjuvant over adjuvant chemotherapy. However, the so-called "internal drug sensitivity test" used in neoadjuvant chemotherapy is not practically feasible. The prospective GeparTrio trial in Germany showed that patients who experienced initial treatment failure received no benefit even when the drug was replaced by a cross-resistant agent. The Aberdeen study prospectively evaluated drug susceptibility in the context of neoadjuvant chemotherapy. The results indicated that when a tumor responded to initial treatment, the pCR increased from 15% to 31% following the switch to docetaxel. Tumors that did not respond to the initial treatment also did not respond to docetaxel (pCR, 2%). These results are consistent with those of the GeparTrio study. Moreover, one-third of tumors that responded to the initial treatment later became unresponsive to the same treatment, and some of these patients may even develop progressive disease. These two prospective studies thus confirmed that the internal drug sensitivity testing used with neoadjuvant chemotherapy is not a reliable predictor of clinical outcome.

We do not deny the benefit of neoadjuvant chemotherapy for some patients with breast cancer. However, overuse of neoadjuvant chemotherapy is not in the best interest of patients. We hope that further research of the appropriate use of neoadjuvant chemotherapy for EBC will lead to a more reasonable consensus regarding neoadjuvant chemotherapy.

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Conflicts of interest

None.

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