If Chemotherapy Is Indicated, Give the Optimal Regimen!

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The 5-year survival data of breast cancer patients have reached outstanding results. Nitz et al. [1] reported a 5-year overall survival rate for the formerly called ‘intermediate risk group’ (patients with 1–3 positive lymph nodes) of 95%, achieved by a modern anthracycline/taxane containing regimen of 4 cycles epirubicin + cyclophosphamide followed by 4 cycles docetaxel. In a combined analysis of 2 intense dose-dense trials Thomssen et al. [2] have previously reported a 5-year overall survival rate of 85 % in patients with median 8 positive lymph nodes by intense dose-dense chemotherapy. As a consequence of the rising numbers of known breast cancer subtypes, ‘modern’ trial designs become more and more restricted for defined subgroups with the aim of targeted therapy. Trials which recruit estrogen receptor-positive/HER2-negative (ER+/HER–) patients investigate the option of chemotherapy deescalation (PlanB trial) or try to define low-risk groups of ER+/HER2– patients by short-time neoadjuvant endocrine pre-treatment and its influence on the decline of Ki-67 proliferation (ADAPT trials) [3]. In the past years we made also improvements in defining low-risk ER+/HER2– patients by the additional use of commercially available molecular tests (Mammaprint®, Oncotype-DX®, Endopredict®, Prosigna®), when all other criteria are inconclusive for therapeutic decision-making. First results of defined low-risk patients in the PlanB and TAILORX trials have shown excellent 3-year and 5-year distant relapse-free survival data with endocrine treatment only [4, 5].

On the other hand, we still have a relevant number of high-risk breast cancer patients, where chemotherapy remains standard of care. Even in 2016, tumor burden (number of positive nodes) remains one of the most important risk factors, not only, but especially in patients with > 3 positive nodes.

If chemotherapy is given to these patients an optimal regimen must be chosen. The Norton-Simon-Hypothesis on log cell kill [6]

suggests that chemotherapy should be given at maximum dosages at minimum intervals. Combination chemotherapy, which always has to make compromises regarding the doses of each drug and treatment intervals due to acute as well as cumulative toxicities, does therefore not comply with this theory. Sequential application of monotherapies, however, allows very high single agent doses and dose-dense treatment intervals. Such dose-dense regimens as well as a meta-analysis [7] have shown higher efficacy in comparison to conventionally dosed chemotherapy, but they did not establish a new standard of care, because the published trials reported controversial results. The design of the individual dose-dense trials shows important differences regarding number of cycles, types of drugs and total dose. In addition, some trials are reported as dose-dense, but present a mixture of dose-dense and conventional schedules. Also the risk profile of the recruited patients differs remarkably between the trials with a median range of tumor positive lymph nodes between 1 and 8.

Considering these differences explains why we have negative and positive trials. Although subgroup analyses are considered as hypothesis generating only, they may have consequences for clinical routine. Only (intense) dose-dense trials, which recruited exclusively high-risk patients, showed a significant benefit for ER+ and ER– patients [8, 9].

In this issue of BREAST CARE results and therapeutic options of dose-dense-trials in the adjuvant, neoadjuvant, and metastatic situation are discussed.

Disclosure Statement

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