Perspective

How transferable are recommendations of the era of treating conventionally defined breast cancer for the era of molecularly characterised breast cancer?

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Breast cancer is not anymore regarded as a single disease, but consists of diverse subtypes that can be defined by using immunohistochemistry. Risk factors that should determine the onset of chemotherapy include positive lymph node status, high histological grade, high proliferation as measured by Ki-67, low hormone receptor status, positive Her2/neu status, and "triple negative" status (1). But, although adjuvant chemotherapy has an important role in patients with early breast cancer in whom the use of chemotherapy is explicitly indicated, its optimal duration has yet to be defined.

In 1990 Fisher and co-workers showed that four cycles of doxorubicin and cyclophosphamide (AC) are equally effective compared to six cycles of cyclophosphamide, methotrexate, fluorouracil (CMF) (2). Several subsequent studies confirmed this approach. The application of AC was generally accepted because of its shorter treatment duration, its better tolerability and an absolute difference in recurrence, breast cancer mortality, and overall mortality at 5 years of 3% compared to CMF (3,4).

Over the time many improvements and new insights in adjuvant chemotherapy have been achieved. In 2005 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis of adjuvant polychemotherapy demonstrated a survival advantage for anthracycline-based adjuvant regimens compared with non-anthracycline-based regimens. In younger women (<50 years of age) with node-positive disease, antineoplastic therapy reduces the risk of recurrence by 37%. In older women (≥50 years of age) in whom the effects of polychemotherapy are not confounded by the anti-endocrine effects of ovarian suppression, antineoplastic therapy decreases the recurrence risk by 23% and 17% in node-negative and node-positive disease, respectively (4,5).

For more than two decades anthracycline containing chemotherapy was the back bone of adjuvant chemotherapy, but a prospective randomized trial comparing different durations of the same chemotherapy schedule and dose was missing. To further resolve this issue Shulman and co-workers conducted a prospective randomized phase III trial using a 2×2 factorial design addressing the two questions (6): (I) whether six cycles of AC are superior to four cycles of AC and (II) whether the mono-therapy of paclitaxel (T) is equally effective to AC, but with reduced toxicity. The primary and secondary endpoints were relapse free survival (RFS) and overall survival (OS), respectively. After a median follow-up of 5.3 years the adjusted hazard ratios for RFS and OS were 1.03 (95% CI, 0.84 to 1.28; P=0.77) and 1.12 (95% CI, 0.84 to 1.49; P=0.44), respectively. Toxicities were as expected. Haematological grade 3 and 4 adverse events were more commonly observed in patients receiving AC and neuropathy was more common in the paclitaxel arms compared with the AC arms. The authors finally conclude that there is no evidence that extending chemotherapy with AC from four to six cycles improves clinical outcome. Of interest, an unplanned subset analysis on the estrogen receptor (ER) and Her2/neu status did not alter the results in favor of six cycles of AC.

In this context it is important to underline the fact that chemotherapy has an ovarian-suppressing effect. It could be

assumed that four cycles of AC might dispose on a smaller anti-endocrine effect than six cycles of AC what might influence the RFS and OS in premenopausal woman.

It has recently been proven that biological heterogeneity influences the benefit from adjuvant chemotherapy. Two investigations using the OncotypeDX®, a 21 gene signature, showed that by defining three risk recurrence groups (low, intermediate and high recurrence score) so far only women with a high recurrence score benefited from the application of chemotherapy (5,7,8).

In order to provide the most appropriate antineoplastic therapy nowadays one should subdivide breast cancer into the distinct breast cancer subtypes luminal A, luminal B, Her2/neu overexpressing and triple negative using clinicopathological criteria (1,9,10). Unfortunately, Shulman *et al*. did not further analyze the effect of different cumulative doses of AC in the diverse breast cancer subgroups. Are four cycles of AC equally effective compared to six cycles of AC in luminal A [ER (+) and/ or PR (+) and not Her/2neu (-) or Ki-67 ≤14%], luminal B [ER (+) and/or PR (+) and Her/2neu (-) and/ or Ki-67 ≥14%], Her2/neu overexpressing [ER (+/-) PR (+/-) and Her/2neu positive] and triple negative [ER (-), PR (-), Her/2neu (-)] breast cancer patients, respectively?

In this context several additional questions have to be solved. Can we define luminal A breast cancers that need to be treated with AC at all? Can we abandon the use of taxanes in luminal B and Her2/neu positive breast cancers? Can we take responsibility for shorter treatment duration in women with Her2/neu positive and triple negative breast cancer?

Data for the comparison of AC versus T have not yet been released from Shulman *et al*.. However, regarding the safety profile of anthracyclines on the one hand and the increasing use of taxanes on the other hand, the role of anthracycline-free regimens should be considered.

In view of the toxicity profile, four cycles of AC recommended by Shulman *et al*. could offer several advantages. Among them, the cumulative dose of anthracyclines is principally not reached. Thus, the associated and feared long term toxic effects - congestive heart failure and leukemia - could be expected to be eventuated less often. And indeed, in Shulman's study cardiac toxicity and leukemias were more frequent in patients receiving sic cycles of AC. But, considering an absolute 3% clinical benefit of 4 cycles of AC compared to CMF and taking into account a risk of cardiac toxicity in 6-26% and the emergence of leukemias in up to 0.5% of patients, respectively, the benefit to risk ratio even for the 6 cycles regimen for AC is relatively small (11).

There is growing evidence suggesting that taxanes are beneficial in the adjuvant setting, irrespective of the patient's age, lymph-node involvement, hormone-receptor expression, and Her2/neu status. Most, but not all, of the efficacy data published to date show a significant improvement in disease-free survival (DFS) for the taxane-based treatment versus the control anthracycline-based treatment. An improvement in OS has only been observed in a few trials (5,12). With regard to Shulman's trial, where the taxane data have not yet been published, it is important to mention that recently two studies were published using anthracycline-free regimens. The US oncology 9735 trial compared AC with docetaxel and cyclophosphamide (TC) and showed an improved DFS in favour of the TC arm with no significant difference regarding OS (13). The BCIRG 006 phase III trial randomized patients to four cycles of AC followed by T, four cycles of AC followed by T and trastuzumab (H), or six cycles of docetaxel/ carboplatin followed by trastuzumab (TCH).The risk-benefit ratio favored the non anthracycline containing TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia (14).

In summary, for the first time Shulman and co-workers present incontestable clinical data that give evidence that the restriction of adjuvant chemotherapy to only 4 cycles of AC was as efficacious and less-toxic than 6 cycles therewith favoring the lower number of cycles. But, whether all subgroups mentioned above will benefit from this treatment choice and which, if any, will benefit from this approach more than another have yet to be identified. Furthermore, we eagerly await the results of the single drug application of paclitaxel compared to AC, because emerging data support the adjuvant use of anthracycline-free regimens. The answers to the same questions raised for AC concerning efficacy and toxicity will be also of interest with regard to the various subgroups of breast cancer for paclitaxel monotherapy.

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