Is It Important to Adapt Neoadjuvant Chemotherapy to the Visible Clinical Response? An Open Randomized Phase II Study Comparing Response-Guided and Standard Treatments in HER2-Negative Operable Breast Cancer

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AUTHOR SUMMARY

ABSTRACT

Background. Neoadjuvant treatment provides a unique opportunity to evaluate individual tumor sensitivity. This study evaluated whether a response-guided strategy could improve clinical outcome compared with a standard treatment.

Methods. Overall, 264 previously untreated stage II–III operable breast cancer patients were randomized to receive either standard treatment (arm A, $n = 131$), consisting of fluorouracil, epirubicin, and cyclophosphamide (FEC100: 500, 100, and 500 mg/m², respectively, for 3 cycles) followed by docetaxel (100 mg/m² for 3 cycles), or adapted treatment (arm B, $n = 133$), beginning with 2 cycles of FEC100 and switching to docetaxel if tumor size decreased by <30% after 2 cycles or <50% after 4 cycles of FEC100 (ultrasound assessments according to World Health Organization criteria). Otherwise, FEC100 was given for six cycles before surgery. Intent-to-treat analysis was performed.

Results. Similar results were observed for clinical response (objective response was 54% vs 56%, $p = .18$), breast conservation surgery (BCS; 67% vs 68%, $p = .97$), and pathological complete response rate (Chevallier classification: 14% vs 11%, $p = .68$; Statloff classification: 16% vs 13%, $p = .82$) between arms A and B. Similar toxicities were observed, even with unbalanced numbers of FEC100 and docetaxel courses.

Conclusion. Adapted and standard treatments had similar results in terms of tumor response, BCS rate, and tolerability. Further survival outcome data are expected. *The Oncologist* 2015;20:243–244

DISCUSSION

One of the important advantages of using neoadjuvant chemotherapy is early identification of unresponsive tumors, providing the opportunity to terminate an ineffective therapy and/or switch to an alternative systemic treatment. We wondered whether an adapted strategy would improve clinical outcome.

Our results demonstrated no significant difference between standard (arm A) and adapted (arm B) treatment based on pathological complete response (pCR) rate (primary end point) (Figs. 1, 2). Moreover, we demonstrated no significant difference in clinical response and breast conservation rate between arms. Similar results have been reported by the Aberdeen [1] and GeparTrio [2] studies showing that switching patients without a tumor response following an initial anthracycline or anthracycline-taxane combination to an alternative (non-cross-resistant) regimen gave a low pCR rate of 2% and 17.7%, respectively. Moreover, Von Minckwitz et al. [4] demonstrated that a strategy of in vivo adaptation treatment

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Figure 1. Study design. The regimen adaptation was done at two levels after two and four cycles of treatment based on a percentage decrease of 30% and 50%, respectively, to define responders versus nonresponders

Abbreviations: FEC100: fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² for three cycles.

did not improve the pCR rate compared with conventional treatment, at 17.7% versus 15.5%, respectively. In the subgroup analysis performed for luminal and triple-negative breast cancer (TNBC), we did not observe a significant difference in pCR rate between arms; however, TNBC achieved a higher pCR rate, with 35% versus 9% for luminal tumors ($p = .002$) in arm A and 42% versus 6% ($p < .0001$) in arm B, using Chevallier's classification.

Two reference regimens for early operable BC, FEC100 (fluorouracil, epirubicin, and cyclophosphamide at 500, 100, and 500 mg/m², respectively, for 3 cycles) and docetaxel (100 mg/m² for 3 cycles), were given in standard and adapted arms, which were scheduled to receive equally 6 cycles of treatment. An imbalance in the number of FEC100 and docetaxel courses was observed because of the adapted strategy beginning with

Figure 2. CONSORT diagram showing the flow of patients for treatment.

Abbreviations: FEC: fluorouracil, epirubicin, and cyclophosphamide; RT, radiotherapy; SBR, Scarff-Bloom-Richardson.

FEC100. The total numbers of FEC100 and docetaxel cycles were 375 and 364, respectively, in arm A and 478 and 262, respectively, in arm B. This did not lead to a statistically significant difference in toxicities, either nonhematological or hematological.

In conclusion, the adapted treatment had clinical results similar to those with the standard regimen in terms of clinical response, pathological response, BCS rate, and toxicities. Further disease-free and overall survival results are awaited.

Author disclosures and references available online.