Does the addition of chemotherapy to adjuvant endocrine treatment add any benefit in ER-positive early breast cancer: can we rely on large randomized control trials in the era of personalized medicine?

The International Breast Cancer Study Group Trial IX (IBCSG IX) is a prospective randomized controlled clinical trial of endocrine versus chemoendocrine therapy in women with postmenopausal lymph node-negative breast cancer [1]. The study was previously reported and published at the median follow-up of 5.9 years showing that patients with estrogen receptor (ER)-positive breast cancer did not benefit from the addition of chemotherapy to tamoxifen (TAM) at that time [2]. Similar findings were in the meanwhile reported by other collaborative groups [3]. This time, the IBCSG IX team is reporting this study at the median follow-up of 13.1 years, comparing adjuvant antiestrogen treatment with combination chemotherapy plus adjuvant endocrine treatment alone according to ER expression. This analysis is limited to 1646 patients of the 1715 randomized, where the ER status is known. All patients had T1a to T3 tumors without any lymph node involvement or metastatic disease. In brief, the study shows that the addition of three cycles of traditional cyclophosphamide, methotrexate, 5-fluorouracil (CMF) to TAM is not beneficial in postmenopausal women with lymph node-negative ER-positive breast cancer; in contrast, chemotherapy is highly effective within the ER-negative cohort. Although data are not surprising today, it is one the studies with the longest median follow-up, and clearly identifying ER positivity as a negative predictor for using chemotherapy, in this case, CMF combination. The study was designed at the time where other predictive markers such as human epidermal growth factor receptor 2 (HER2), progesterone receptor, and Ki67 were not always available. In the interim, of course, HER2 and other molecular markers were identified to be predictive of responsiveness to systemic treatment. Other shortfalls, which could have been avoided but are discussed in the manuscript, is the choice of three versus six cycles of chemotherapy, duration of tamoxifen administration, different methods of ER measurements, changing the definition of ER-positive breast cancer, and of course, lack of use aromatase inhibitors that were not available in the adjuvant setting at that time. The long-term observation of subjects on study lead also to a critical evaluation of long-term toxicity and side-effects: CMF, according to study results, had no influence on the incidence of second non-breast malignancies or deaths without a cancer event. Among patients in the two cohorts, 6.8% on CMF had a second non-breast malignancy compared with 6.5% in the TAM alone group, and deaths without prior cancer event were 7.2% and 5.9%, respectively.

Most importantly, multigene markers were not available at the time of design of the study. A number of prognostic multigene tests have been established in the meanwhile that have the potential to be prognostic for outcome (Oncotype™; MammaPrint®, Mammaprast®, PAM50) [4–7] and sometimes predictive for choice of therapy.

At this point in time, planning and conducting large randomized prospective studies in breast cancer will not be feasible anymore, unless patients are stratified or selected for specific biologic features of breast cancer. This could be done simply by ER, progesterone receptor, and HER2 or by the intrinsic subtypes [7] that can be measured now (albeit not validated clinically yet). A number of such tests are now commercially available and even more such tests are currently being developed in preclinical and early clinical stages. Only with such modern approach, we will learn more and make some additional step to improve outcomes of patients with breast cancer.

S. Gluck*

Department of Medicine, Division of Hematology-Oncology, Sylvester Comprehensive Cancer Center, University of Miami Leonard M. Miller School of Medicine, Miami, USA

(*E-mail: sgluck@med.miami.edu)

disclosure

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