Guest Editorial

Squaring the Circle: Adjuvant Chemotherapy for Older Women With Breast Cancer

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ADJUVANT chemotherapy—that is, chemotherapy after surgery in women at high risk for recurrence—has reduced by 21% the breast cancer-related mortality in patients aged 50 and younger (1). The benefits of adjuvant chemotherapy seem to fade with age and are not detectable for women aged 70 and older, according to the meta-analysis of randomized controlled trials performed by the Early Breast Cancer Trialists’ Collaborative Group (1). Admittedly, only 1044 of the more than 75,000 women included in the meta-analysis (a number clearly insufficient to detect significant survival difference) belonged to this age group. The issue is consequential, as 30% of breast cancers occur in women 70 years old and older (2).

The study by Du and colleagues (3) in this issue of the Journal presents important new information related to adjuvant chemotherapy in older women. Utilizing the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Medicare files, the authors were able to track the outcome of 6190 women aged 65 and older, of whom 4024 were 70 and older. They found that adjuvant chemotherapy reduced the relative risk of breast cancer death among those aged 65–69, but not for those older.

Du and colleagues should be congratulated for a number of reasons. The first is the approach to the problem; to my knowledge, it is the first time that the SEER–Medicare database has been tapped to study treatment outcome. In the past it had been utilized primarily for exploring patterns of care and preventative interventions (4,5). The present study indicates a new and effective avenue for establishing the impact of treatment of common conditions in elderly women. In addition, the database allowed the authors to relate comorbidity to the chance of receiving treatment and to survival, an issue of major concern. Of special interest is the sensitivity analysis to explore the effects of unknown confounders on treatment outcome, which is especially relevant for the older patients, for whom not all predictive factors of death and functional decline might have been yet identified. It was found that a 30% or higher difference in prevalence of one of these cofounders between the treated and untreated groups may be responsible for the difference in outcome. This is a new and creative way to explore the reliability of the information related to management of older individuals, especially the oldest old.

In addition to demonstrating the application of a novel and innovative research methodology, what are the implications of this important study? This question is twofold as it involves both the clinical and the research arenas. From the clinical standpoint, the main issue is whether women aged 70 and older should receive adjuvant chemotherapy outside of a clinical trial. It is important to appreciate that Du and colleagues don’t even try to make this suggestion! Rather, they recognize that no final conclusions may be drawn from their data related to the benefits of adjuvant chemotherapy in the oldest patients, as different forms of chemotherapy were used, the dose intensity delivered was unknown, and it was unknown whether treated and untreated patients were comparable in terms of disease stage, function, and comorbidity. On the research side, a number of randomized controlled studies have shown that adjuvant chemotherapy delays the recurrence of breast cancer and prolongs the survival of postmenopausal women with involved axillary lymph nodes (6–8). From these data it is reasonable to infer that women aged 70 and older, with adequate life expectancy and high risk of recurrence, may benefit from adjuvant chemotherapy. There is no apparent biological reason to consider age 70 as a cut-point beyond which adjuvant chemotherapy ceases to work. The decision whether to utilize this form of treatment should be based on individual risk/benefit assessment (9,10). A recently developed computer program, available free on the web (at www.adjuvantonline.com) allows this assessment to be estimated accurately (10).

The main challenge in the research arena is how to conduct randomized clinical trials of adjuvant chemotherapy in older persons, in particular, how to select eligible patients and whether there should be an untreated control group. Clearly, patient selection should be primarily dictated by the expected benefits of chemotherapy, and these should be of such an order of magnitude to allow for detection of meaningful differences between the experimental and the control group. In older individuals, this assessment clearly involves estimate of life expectancy and tolerance of chemotherapy. This approach represents a departure from classical clinical trials in which patients have been randomized and stratified according to predictive and prognostic factors, such as tumor size, histologic differentiation, hormone-receptor status, and number of involved
lymph nodes, with little or no attention to life expectancy, risk of functional decline, social support, or cognition. As for the untreated control group, this is probably unrealistic in the United States at present, but a comparison between a mild and a more aggressive form of treatment represents a reasonable approach. This approach has been followed by the Cancer and Acute Leukemia Group B (CALGB) in an ongoing trial comparing the oral agent capecitabine with combination chemotherapy in women aged 65 and older with breast cancer and positive lymph nodes (11).

Another research issue that deserves attention includes potential age-related changes in tumor biology. The meta-analysis showed that the benefits of adjuvant hormonal therapy persist throughout all age groups, even after age 70 (1). This observation has important implications:

1. The decline in the effectiveness of chemotherapy cannot be accounted for by competing causes of death, as they would affect as well the efficacy of hormonal therapy.
2. Possible explanations for the declining effectiveness of chemotherapy include inadequate doses of chemotherapy and declining sensitivity of the tumor to chemotherapy. This last hypothesis has never been addressed.

In conclusion, Du and colleagues have provided an important contribution to the field, by: (a) demonstrating that adjuvant chemotherapy does not have a substantial impact in breast cancer-related mortality for women aged 70 and older and (b) providing a demonstration of a very creative use of the SEER–Medicare database. Their study has also outlined the questions that should be addressed in future clinical trials, and has suggested a more comprehensive approach in the assessment of patient eligibility for these trials. What concerns clinical practice is that the study reaffirms the need for individualized decisions based on patients’ life expectancy and functional reserve.

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