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Editorial

EDITORIAL

Adjuvant Chemotherapy for Older Patients With Breast Cancer: When Is the Pain Worth the Gain?

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Although many older patients with breast cancer develop indolent, early-stage disease for which chemotherapy is not anticipated to improve survival, a subset has higher-risk disease that is chemotherapy responsive. From the limited data we have available—albeit mostly from registry-based or pooled secondary analyses—patients across the age spectrum derive a consistent relative benefit in breast cancer–specific survival from chemotherapy (1–3). Among older women, this apparent benefit is mainly driven by reducing recurrences in individuals who have low competing risks and high short-term risks of recurrence. The benefit-risk balance is complex in clinical practice among older patients because chemotherapy-induced toxicity is worse, and the benefits are not as well defined as those anticipated in younger individuals (4,5) .

Gene expression profile (GEP) testing, such as Oncotype DX, has provided a platform to quantify the risks of recurrence and the potential benefits of chemotherapy in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative breast cancer. This approach is now used widely to tailor decision making and limit chemotherapy exposure when the anticipated benefits are small or negligible. Unfortunately, data on Oncotype DX in older women are sparse, and retrospective analyses of scores by age are limited by selection bias (6), where clinical risk thresholds to send GEP testing are consistently higher than in older vs younger patients.

In this issue of the Journal, Chandler and colleagues simulated the benefits of chemotherapy in older patients with tumor recurrence scores of 26 and higher in stage I and IIA disease while accounting for comorbidity and competing causes of death (7). Not surprisingly, their robust models suggest that the magnitude of "gains," defined as quality-adjusted life-years, from chemotherapy in early-stage disease decreased with increasing age and comorbidity. They concluded that "GEP testing (and chemotherapy use) should be reserved for women aged 75 without severe comorbidity." Further, only small benefits of chemotherapy were seen for those ages 65–74 years with no/low or moderate comorbidity.

The results from this simulation have face validity and are consistent with expectations, given what we know about the prognosis with hormonal therapy alone in the setting of stage I and IIA HR+ breast cancer as well as the concerns for toxicity and competing causes of death for older patients (8,9). There are, however, some limitations in their model beyond those mentioned. The assumptions for breast cancer–specific survival without treatment are derived from a model that was not highly inclusive of older patients (10). In addition, although data were extrapolated from TAILORx (11) for the model, no patients enrolled in this study were older than 75 years. The incorporation of treatment toxicity is a strength of this simulation analysis, but the authors used claims-based datasets to estimate rates of toxicity and focused on hospital events only. How the authors accounted for the impact of toxicity on short- and longer-term morbidity is not well defined. Finally, the selection of a score of 26 as the threshold for chemotherapy benefit is practical but potentially problematic given the poorly defined benefit of chemotherapy for those whose scores fall in the 26–30 range.

Despite the potential limitations of Chandler and colleagues' model, these simulated data provide more reassurance that older patients with low anatomical risk can appropriately be treated without chemotherapy and should not have GEP testing. That said, even without the simulation, if one assumes a 30% reduction in the relative risk of distant recurrence reduction (12) for those with "high" Oncotype DX scores, the absolute risk reduction in stage I or IIA disease will be small to modest at best, with rare older patients anticipated to meaningfully benefit. In this clinical setting, we should be focusing on endocrine therapy alone and addressing barriers to longer-term adherence. However, in stage III HR+ disease, as well as in older patients with triple-negative or human epidermal growth factor receptor 2–positive cancers, there remains considerable uncertainty about the optimal treatment approach among older patients

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with and without advanced comorbidity; the simulation model by Chandler and colleagues does not address such patients.

To make simulations more meaningful, we need prospective data from discrete subsets of patients who are most likely to benefit from treatment but who may have conditions that put them at risk for functional and clinical deterioration. As an important starting point, we now have multiple validated models (13–15) that powerfully predict for grade 3–5 toxicity events in those age 65 years and older in the setting of chemotherapy for solid tumors and neo/adjuvant chemotherapy for breast cancer specifically. These prediction models are based on prospectively collected patient data derived directly from clinical and geriatric assessment variables in older patients and provide powerful, individualized information on who is at most risk for severe adverse events during chemotherapy.

Despite having this valuable information, we are still in need of additional strategies to help balance this information with the anticipated treatment efficacy and how upfront or subsequent dose modifications (used to mitigate toxicity) may affect both disease and quality of life outcomes. We also need further insights into patient preferences of older individuals with breast cancer. Obtaining these prospective data will take coordinated efforts. This work should be prioritized if we are going to address these unanswered questions for a growing patient population with an increasing need for level I evidence to inform their care.

Notes

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