Nonhormonal Systemic Therapy for Advanced Breast Cancer: Do the Math!
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Since the founding of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) 25 years ago (1), early breast cancer trials encompassing all aspects of operable breast cancer management have been compiled to produce individual patient data meta-analyses at 5-year intervals. The EBCTCG overviews have quantified the impact of adjuvant polychemotherapy, tamofoxifen, ovarian suppression/ablation, and radiation on overall survival (OS) and disease-related events (2), informing widely used evidence-based clinical practice guidelines (3,4) and contributing to the ongoing decline of breast cancer–related mortality in Western societies (5). The most recent cycle of the EBCTCG overview includes data from more than 661,000 patients with early breast cancer who were randomly assigned across 823 clinical trials (5).

Advances in systemic therapy for metastatic disease, however, have been more difficult to characterize. Head-to-head trials in the metastatic setting typically involve far fewer patients and have limited power to detect potentially meaningful differences in survival and toxicity (6). Prior attempts to synthesize the literature, including a recent overview of individual patient data from trials investigating the first-line use of taxanes, have been hampered by the lack of a common comparator across trials and have failed to consistently demonstrate survival advantages for particular therapeutic regimens (7–9). With many available agents demonstrating activity, widespread consensus does not exist regarding the optimal dosage, timing, sequence, or combination of available therapies.

In this issue of the Journal, Mauri et al. (10) provide a meta-analysis of survival data based primarily upon indirect comparisons from 128 trials involving 26,031 advanced breast cancer patients treated with nonhormonal systemic therapies. In contrast to a traditional meta-analysis that directly compares two interventions by pooling data only from trials asking a similar question, such a so-called network meta-analysis also incorporates indirect comparisons of multiple interventions from trials that differ widely in design using a statistical methodology that respects random assignment (11).

Using this approach, the authors were able to quantify the survival gains of 21 different classes of therapy relative to older single-agent therapies chosen as the reference standard. The main finding of their labor-intensive work is that many classes of modern breast cancer therapy, including anthracyclines, taxanes, novel nontaxanes, and trastuzumab, either as monotherapy or as combination therapy would produce tangible gains in absolute survival over older single agents, ranging from 4.2 to 12.5 months for a patient with an anticipated survival of 1 year treated with the reference standard alone.

This study provides an important historical perspective and a framework for interpreting future advances in breast cancer therapy. Nevertheless, it has a number of limitations that should be acknowledged. A key underlying principle of network meta-analysis is that relative treatment effects are the same across trials independent of the comparator. To support this assumption in their dataset, the authors examined statistical heterogeneity across direct comparisons in their network and found a large degree of statistical heterogeneity in only five of 45 direct treatment comparisons. However, many of the examined treatment comparisons involved too few patients to rule out the possibility of substantial underlying intertrial variability, as it is known that such heterogeneity tests lack statistical power. Likewise, in situations where both direct and indirect comparisons between treatments are available, it is important to analyze the degree of incoherence, or disagreement, between direct and indirect comparisons. The authors found modest incoherence in only one closed loop of their network, but tests of many loops were underpowered to reliably rule out the possibility of potentially meaningful incoherence in their network. Although prior empirical studies demonstrate that indirect comparisons usually agree with the results of head-to-head randomized trials (12), notable exceptions have been reported, for example, in trials to determine the best initial highly active antiretroviral therapy for patients with HIV infection (13).

Ultimately, their analysis is predicated upon the assumption that trials with older single agents no longer in widespread use are
comparable to more recent ones testing novel agents. However, recently more stringent patient selection criteria to enrich for patients likely to respond to targeted therapies have been used. For example, recent trials with trastuzumab enrolled only patients with overexpression and/or amplification of the HER-2 receptor, which accounts for approximately 20% of advanced breast cancers. Whether survival advantages detected in these selected populations can be compared with those seen with older single agents tested in unselected populations in a clinically meaningful manner is questionable.

When a number of treatment options exist for the practicing clinician, an important goal of a mixed treatment comparison is to provide a hierarchy of effect that can be used to guide treatment decisions (14). The authors of this network meta-analysis appropriately conclude that “several regimens have shown effectiveness, and for some of them the treatment effects are practically indistinguishable in magnitude.” Because systemic therapy for advanced breast cancer is palliative in nature, any gains in survival must be balanced against potential toxic effects, impact on patient-rated quality of life, and the additional financial burdens of therapy. Although the combination of novel nontaxane agents and a taxane produced the greatest absolute survival gain over older single agents in this meta-analysis, it is premature to conclude that this should be the preferred first-line treatment regimen. The reported efficacy of this combination is based upon three trials testing this combination against taxane monotherapy (15–17). All three trials demonstrated a statistically significant improvement in favor of the combination regimen, with very few patients in the upfront taxane monotherapy arm receiving the novel nontaxane agent following progression in two of these studies (15,16). This raises the question as to whether the observed survival gains would be the same in a setting where patients may have access to additional systemic therapies upon progression, particularly in light of the additional toxicity with combination therapy (18).

The finding from this network meta-analysis that most regimens demonstrated similar relative efficacy in first and subsequent lines of therapy provides indirect support for the widespread practice of sequential single-agent therapy for the majority of patients with advanced breast cancer. The choice of particular agents, along with the decision of when to use combinations of therapy, must be individualized on the basis of patient-related factors, such as disease-free interval, the burden of metastatic disease, prior adjuvant therapies, and patient preference.

With the development of many active lines of systemic therapy, clinical trials in advanced breast cancer have increasingly adopted progression-free survival (PFS) rather than OS as the primary endpoint. Regulatory agencies have followed suit, accepting gains in PFS as the basis for approval of novel agents (19,20), despite a lack of evidence to support PFS as a surrogate for OS (21). How such studies with a PFS endpoint can be integrated into a network meta-analysis with older studies to inform decision making will be an important subject of future research.

Although this network meta-analysis is unlikely to alter routine clinical practice, it provides a solid evidence-based foundation to support the observation that the survival of women diagnosed with advanced breast cancer has improved because of more active systemic chemotherapy and targeted therapy (22–25). This should provide hope to patients, investigators, industrial sponsors, and regulatory agencies alike that well-designed clinical trials with novel systemic therapies can further alter the natural history of this devastating disease.

References

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