The oncology community has known for more than 30 years that anthracycline-containing chemotherapy improves disease-free and overall survival in patients with breast cancer (1). Despite this, physicians are often reluctant to use it in certain “high-risk” groups, such as the elderly, due to concerns over the risk of short- and long-term cardiotoxicity. Although the risk of cardiotoxicity is dose dependent (2,3), it has been hard to predict which patients are at greatest risk for developing complications from treatment.

Randomized clinical trials are excellent for establishing the efficacy of new therapies by comparing experimental and standard therapies. However, many patients do not qualify for the rigorous entry criteria of most trials, and, thus, the effectiveness of these treatments, or how they work in the “real world,” often needs further clarification, usually with the use of observational studies. Furthermore, determination of the long-term effects of treatments can be more of a challenge. Long-term toxic effects in particular are often rare, necessitating the evaluation of large numbers of patients with observation and follow-up for years following completion of primary treatment. To evaluate this prospectively would be prohibitively expensive. Patients who are enrolled in clinical trials are often healthier than those treated in the community, so risk estimates are often hard to generalize. Therefore, observational studies, using sophisticated epidemiological methods, are usually used to characterize risk and predictors of late effects in the community.

A novel and popular recent approach has been to use large administrative databases to evaluate the long-term complications of treatment. One database that has been of particular value has been the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database, which contains clinical, demographic, and medical claims data on patients aged 65 years and older diagnosed with cancer since the early 1990s. The SEER–Medicare database is invaluable for studying unanticipated treatment effects and long-term outcomes in a population-based sample of patients who, for various reasons, have been underrepresented in clinical trials (4). Given the constraints on eligibility for clinical trials and other barriers to trial participation, analysis of such databases is the only way to find out how treatments work in the real world.

Using the SEER–Medicare database, the risk of congestive heart failure following anthracyclines has been characterized for women with early-stage breast cancer (5,6), and for patients with non-Hodgkin lymphoma (7). For each of these analyses, those with prior heart disease were less likely than others to receive anthracyclines, and known cardiac risk factors were associated with increased risk of congestive heart failure. Only hypertension was found to actually potentiate the risk of anthracycline-induced congestive heart failure (7). Although these studies were strengthened by large numbers of subjects and up to 10 years of follow-up, they were limited by a lack of anthracycline dose information in the database and by the diagnosis of congestive heart failure being determined only through billing claims.

In this issue of the Journal, Ryberg et al. (8) use data from about 1000 patients with metastatic breast cancer seen at their institution over a 20-year period to develop a predictive assay for cardiotoxicity with the anthracycline epirubicin, which, on a milligram-per-milligram basis, causes less cardiotoxicity than doxorubicin. This study has the pluses and minuses of single-institution studies, with smaller numbers and less ability to be generalized than database studies but with much more detailed information on each subject. Unlike prior studies that evaluated the dose–toxicity relationship in women with metastatic breast cancer (9), this study has the advantage of controlling for competing causes of mortality, performing a time-dependent analysis, and controlling for other factors that are known to increase risk of congestive heart failure. In this analysis, the total dose of anthracycline was available. Furthermore, in contrast to the database studies, the outcome (ie, congestive heart failure) was defined by both clinical and objective criteria.

Like some other recent studies on predictive models (10), the analysis of Ryberg et al. (8) takes into account a number of known factors associated with risk, including age, prior cardiac disease, known cardiac risk factors, thoracic radiation, prior hormonal therapy, and prior cyclophosphamide–based chemotherapy. As one would expect, some of these known risk factors for congestive heart failure in the general population are also associated with risk in patients treated with epirubicin. It is unclear from this analysis, however, whether any of these factors potentiate the effects of epirubicin or whether their effects are purely additive. Furthermore, the association between prior hormonal therapy and risk of congestive heart failure is not consistent with other studies in the literature and deserves additional confirmation.

Interestingly, the authors calculate the maximum dose that would result in no more than a 5% rate of congestive heart failure for a variety of clinical scenarios for patients of different ages. Maximum doses ranged from 300 to 900 mg/m² as a function of the patient’s personal risk factor profile. Given the large number

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of therapies currently available for metastatic breast cancer and the competing causes of mortality, these results may have more relevance to women with early-stage cancer, who often receive anthracyclines as part of their adjuvant therapy and who are likely to be cured from their cancer. When extrapolated, this analysis provides useful information, that in patients who fit a high-risk profile may be the best candidates for non–anthracycline-based regimens. It must be kept in mind, however, that for patients with early-stage breast cancer, a 5% rate of congestive heart failure may be considered unacceptably high.

We have learned in the treatment of cancer that “one size does not fit all.” We have moved into an era of personalized medicine in which we can predict response to treatment based on genetic profiles of tumors and on variation in drug metabolism. One example is Oncotype DX, the 21-gene profile that can predict recurrence risk and response to treatment (11). Prediction of risk for late effects is within reach as well, because individual variation also affects toxicity. For example, the UGT1A1, CYP2D6, and DPD polymorphisms are being incorporated into treatment decisions as factors that contribute to treatment-related complications (12).

Numerous studies have shown that a substantial number of patients do not receive standard, life-saving treatment for a variety of cancers (13–15). Fear of toxicity is one major reason for avoiding such therapy. If we can better predict who is at greatest risk for toxicity and who is not, we may be able to comfortably offer standard treatment to a larger percentage of the population. Ideally, in the era of individualized medicine, future models will take into account clinical factors, tumor characteristics, disease risk factors, and genetic factors to integrate contributions to both risk and benefit. Ultimately, this approach will allow us to identify patients at the greatest risk of adverse treatment effects, to find ways to reduce that risk, and to improve the quality of life of the rapidly growing number of cancer survivors.

References


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