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Meta-analysis: Should It be More Than the Sum of Its Parts?

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In this issue of the Journal, Bonilla et al. (1) present the results of what the authors call a systematic review and meta-analysis of dose-dense chemotherapy in nonmetastatic breast cancer. The rationale for dosing chemotherapy at shorter intervals ("dose-dense" chemotherapy) is based on Gompertzian kinetics, as described by Norton et al. (2). This mathematical model predicts that tumor doubling time decreases with increasing tumor size. Conversely, tumor cells grow faster as the tumor burden decreases with the initiation of chemotherapy (2). Dose-dense chemotherapy is predicted to attack rapidly dividing tumor cells more effectively compared with the conventional dosing schedule. The safety and feasibility of dose-dense chemotherapy dosing were first demonstrated in a pilot phase II study that used an anthracycline-based chemotherapy agent with growth factor support (3). The results were validated in a large phase III trial, the cancer and leukemia group B (CALGB) trial 9741, which showed better clinical outcomes in the dose-dense arm when using an anthracycline and taxane-based chemotherapy regimen (4). Since this landmark trial, the dose-dense regimen has been widely adopted in clinical practice. It is important to distinguish the concept of dose density from dose intensity. Dose intensity is defined by the amount of treatment delivered per unit of time (5). For example, 60 mg/m^2 of doxorubicin given every 3 weeks results in a dose intensity of 20 mg/m^2/wk. Multiple other studies comparing frequent dosing with conventional dosing schedule have been published in an attempt to validate the results published by Citron et al. (4) for CALGB 9741. Some of these studies are included in the article by Bonilla et al. (1) and are discussed.

Meta-analysis is a statistical combination of results from two or more separate studies on a specific subject (6). The purpose of the meta-analysis is to estimate the effect size by means of the weighted average. The advantages of meta-analysis include higher statistical power than a small individual study; a meta-analysis also allows for generalizations to the studied population. However, meta-analysis has several potential weaknesses. Even a statistically

well-performed meta-analysis of inadequate or heterogeneous studies results in skewed or incorrect conclusions. In addition, various kinds of biases can distort the results. For example, the so-called "file drawer problem" is caused by inclusion of published data only in a meta-analysis and results in biased effect sizes. No one knows how many studies have been conducted on a given subject but never published because it may be difficult to get negative results published (7). Another example of a possible source of bias is the Simpson paradox, in which a correlation that is present in different groups is reversed when the groups are combined. This result is due to unequally sized groups being combined in the same dataset, causing an incorrect weighing of the results (8). Furthermore, "cherry picking" of the studies may produce biases when performing meta-analyses.

Examples of well-performed overviews are the publications by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). This group was established in 1985 to collect raw data on all women who have been randomly assigned in trials for the treatment of operable breast cancer. The updated analyses are published every 5 years and include results of adjuvant endocrine therapy, chemotherapy, ovarian ablation, and radiotherapy. The purpose of EBCTCG overview analyses is not to impose any particular interpretation or method of analysis of the trial results, but rather to derive informative conclusions from an appropriate overview of many trial results. However, some readers may prefer to review only a limited number of the trials. Similarly, the data from each separate trial are available in sufficient detail to permit alternative analyses. Thus, one of the main functions of the EBCTCG is to make available unbiased data from all of the relevant randomized trials in early-stage breast cancer to facilitate the construction and publication of various different interpretations of the trial results (9).

The stated goal of the study by Bonilla et al. (1) is to investigate the efficacy and toxicity of the dose-dense chemotherapy in early-stage and locally advanced breast cancer by performing a systematic review and meta-analysis on the subject. One of the strengths of the study is that the authors choose survival as an endpoint. To reduce the heterogeneity among the studies, the authors perform subgroup analyses on what the authors call conserved and modified dose-dense studies. The conserved chemotherapy group consists of studies that compare the same chemotherapy regimens, one with a standard schedule and the other with dose-dense schedule. In this subgroup of only three studies, the analysis of the heterogeneity is adequately carried out. However, the fact that the study by Venturini et al. (10) is underpowered may have an impact on the meta-analysis conclusions. The results of the modified dose-dense group are very difficult to interpret. In this group, the individual studies have important differences between the study arms with respect to chemotherapy agents, sequence, and dosing, which introduce other variables. For example, four of the studies (11–14) have different chemotherapy agents in the study arms. Two studies (15,16) have the same agents in the study arms, but one arm has concurrent dosing and the other sequential dosing. One study (17) is testing both dose density and dose intensity. In addition, instead of having a survival endpoint, the study by Von Minckwitz et al. (12) measures the rate of pathological complete response in the neoadjuvant setting. Finally, the fact that a pooled analysis of all 10 studies is performed negates the possible benefits gained from the authors' attempt to make the study groups more homogeneous in the subgroup analyses.

Anthracycline and taxane-based dose-dense chemotherapy is very effective in the adjuvant treatment of breast cancer. The results of National Surgical Adjuvant Breast and Bowel Project trial B-38 comparing TAC (docetaxel, doxorubicin, and cyclophosphamide) with dose-dense AC (doxorubicin and cyclophosphamide) followed by T (paclitaxel) and dose-dense AC (doxorubicin and cyclophosphamide) followed by TG (paclitaxel and gemcitabine) will further elucidate the chemotherapy choices in the adjuvant setting (www.clinicaltrials.gov: NCT00093795). Future challenges include incorporation of biological agents, such as bevacizumab and HER2-targeted therapies into dose-dense regimens (18,19).

Although Bonilla et al. (1) apply appropriate statistical methods in their meta-analysis, the variability among the individual studies makes it impossible to draw strong conclusions. Except for the study by Citron et al. (4), none of the articles included in this meta-analysis truly measure the impact of dose density. A systematic review on this subject without meta-analysis would have provided an overview on this subject and at the same time avoided important study biases. Approaches such as EBCTCG overviews allow for more unbiased and flexible ways to interpret data from multiple individual studies. Unfortunately, this meta-analysis adds little to the body of evidence regarding the effect of dose-dense chemotherapy on survival.

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