Reporting of Adjuvant Breast Cancer Trials: When Is the Right Time?

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The article by Joensuu et al¹ published in *Journal of Clinical Oncology (JCO)* is an example of the timely reporting of an adjuvant breast cancer trial adding oral capecitabine to standard chemotherapy. Although there is no effect in the whole trial population, subgroup analysis demonstrates a statistically significant benefit for the addition of capecitabine in triple-negative patients, an interesting result first presented at the American Society of Clinical Oncology Annual Meeting in Chicago, IL, in 2010.² However, this is not the first time the Finland Capecitabine Trial, also known as FinXX, has been presented. It was reported in full in *Lancet Oncology* in 2009,³ and at that point, capecitabine showed a benefit for the whole population. How can the result of a trial change? Has it really changed, or was the earlier report simply premature? The most likely conclusion is the latter, which raises questions about the right time to report trial results.

As a lead clinician on adjuvant and neoadjuvant breast cancer trials over the past 15 years,^{4,5} I have slowly and rather reluctantly (on my part) been schooled in patient perseverance, not only with regard to what is required to complete large trials, but also in terms of waiting for that all-important first analysis. Gregory et al⁶ published on the dangers of early reporting in a fascinating analysis of adjuvant breast cancer data and demonstrated the misleading results of early and repeated analyses. Only as time passed and follow-up matured did the survival curves become stable and provide a robust estimate of progression-free (PFS) and overall survival (OS). Is that what has happened here? Were the initial positive data simply the results of a few random events overly influencing the curves? If so, how do we assess the right time to report and incorporate results clinically?

In adjuvant breast cancer trials, there is another complication resulting from the enrollment of patients with different subtypes of disease associated with different natural histories. This may be more widespread in breast as opposed to other cancers. Blows et al⁷ have, in an elegantly simplified analysis using immunohistochemistry in more than 10,000 breast cancers, demonstrated how different these populations are with regard to the shapes of their PFS and OS curves. After publication of these data, the group is now using the same immunohistochemistry set to examine the NEAT (National Epirubicin Adjuvant Trial)⁴ translational tumor bank. We are particularly interested in investigating when adjuvant chemotherapy has maximum effect (benefit) in the various subgroups. Just as the PFS and OS curves have different shapes (early fall and then leveling off in high-risk popula-

tions, compared with slow and steady decline in better-risk populations), so it has been shown by Berry et al⁸ that the differential benefit of additional chemotherapy is seen earlier in high-risk populations. Analysis of the type described will require repetition with longer follow-up, because only then will the long-term benefit of the treatment to the whole breast cancer population be apparent. Analyzing the different subgroups and the differential, time-dependent effects of chemotherapy will require collaborative meta-analysis to achieve the necessary numbers. For clinical trialists, this suggests that the accrual of patients with subtypes of breast cancer should be preplanned and adequately powered prospectively to allow independent analyses. Alternatively, clinical trials should be restricted to specific subtypes.

The enrollment of patients from different subgroups that experience differences in the timing of the effects of chemotherapy could indeed be an explanation here. In the earlier analysis of the FinXX study,³ events were more likely in the high-risk population, and therefore, early reporting would contain more information from the high-risk population. This is borne out by the subgroup analysis in the triple-negative population in the present report,¹ which does continue to show benefit for the addition of capecitabine. In summary, there is a risk in reporting trials too early that a positive result may simply be either the play of chance or the emergence of a predominant effect/benefit in a high-risk early-relapsing population, and clinical trialists and statisticians need to consider these issues prospectively as they plan trials and their analyses and reporting.

We must applaud the authors as well as *JCO* for publishing what is now a trial with an essentially negative result. Whatever is stated in editorials and review articles, there remains a strong bias for positive-results reporting, whereas equally significant but negative results continue to face publication challenges. We should acknowledge the temptation to look early and publish quickly if results are positive, but trialists should resist this, as should journals.

It is clear that timely reporting of large randomized phase III adjuvant breast cancer trials can be an ethical imperative when life-saving treatment may be made available earlier, but we have an equal imperative to avoid the harm that would occur from broad adoption of what are ultimately shown to be ineffective therapies. The right time for that important first analysis must be decided carefully on an individual trial basis, by chief and principal investigators and biostatisticians working on the trial. In addition, we should recognize that the current biostatistical concern is simply another manifestation of our

increased understanding of the molecular biology and natural histories of the several common breast cancer subtypes. If we acknowledge that they represent different diseases with different natural histories, we can then plan to analyze treatment effects in subtype-specific ways, which will generally be at different time points. At the same time, the reporting of negative results should be encouraged.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Should All Women With Breast Cancer Be Tested for *BRCA* Mutations at the Time of Diagnosis?

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Goodwin et al¹ ask whether or not, among women with breast cancer, the presence of a *BRCA1* or *BRCA2* mutation is of clinical significance. They propose that information about prognosis can help women make better informed decisions regarding cancer treatment, preventive surgery, and screening. If so, these are excellent reasons to know one's genetic status, and these are issues that concern many of us. In terms of screening, the patient with a mutation can ask: "If I develop breast cancer and it is identified by magnetic resonance imaging (MRI) screening, will the prognosis be so good that I am nearly assured of a cure?" If so, then prophylactic surgery may be unnecessary. Burness and Olopade² ask us to believe that this is now the case. However, in the Goodwin et al paper, 27% of the women with cancers below 2 cm in size and 18% of the women with node-negative hereditary breast cancers experienced a distant recurrence in the 8 years of follow-up. For noncarriers with small cancers, the equivalent proportion was 15%. Among *BRCA1* carriers, 31% of those with a tumor of 2 cm or less and 20% of those with node-negative breast cancer died in the follow-up period (we do not know how many of these were screen detected). The beneficial effect of chemotherapy on survival in patients with hereditary breast cancer, in particular those with a *BRCA2* mutation, was strong—even if the breast cancer was small—and the authors warn us that "caution should be exercised in withholding adjuvant chemotherapy in the face of favorable tumor characteristics in *BRCA1* and *BRCA2* mutation carriers."¹ This seems a prudent recommendation and is in keeping with earlier observations.³⁻⁵ By extension, one cannot recommend MRI surveillance with the hope that chemotherapy can be avoided if the cancer is caught early enough.

Because there is an historical study, Goodwin et al evaluated the chemotherapies in use at the time (1995-2000). Approximately 60% of the treatments included an anthracycline. The data support the contention that these patients tend to be responsive to conventional chemotherapy and it is hoped that with some new regimens (such as poly ADP ribose polymerase inhibitors) and some old regimens (such as cisplatin) the response might be even better.^{6,7} Byrski et al⁷ reported a pathologic complete response to neoadjuvant cisplatin in 10 of 12 Polish women with a *BRCA1* mutation. They restricted their study to *BRCA1* carriers because they did not have access to *BRCA2* carriers. It is important to evaluate cisplatin for patients with breast cancer with a *BRCA2* mutation in light of these observations and those of Goodwin et al. An interesting case report of a patient with pancreatic cancer and a *BRCA2* mutation who showed a dramatic response to cisplatin was recently published.⁸

The paper tells us little about different surgical approaches (ie, the authors do not compare the survival of women with lumpectomies with those with mastectomies). In any case, 7.9 years is too short to compare the two approaches. This is because for evaluating chemotherapy, we are comparing the number of deaths from the first cancer, but for surgery (eg, contralateral mastectomy) we are comparing the number of deaths from second primary cancers. Most women who die of a second primary breast cancer will do so in the second decade of follow-up, and it is inappropriate to judge in favor of mastectomy (or lumpectomy) based on only 8 years of follow-up.⁹ The risk of ovarian cancer is sufficiently high after a