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Editorial

The Potential Lack of Comparability Between Interim and Final Results of Cancer Clinical Trials

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Clinical research has as its major goal the discovery of improvements in cancer therapy which when applied by the general oncologic community will decrease the mortality and/or morbidity of cancer. The findings of clinical research are made available to the oncologic community through publication in peer reviewed journals and presentations at scientific symposia and meetings. A clinical research experiment takes years to plan, execute and analyze totally. It is not uncommon for a protocol study to take one to two years to accession the minimum number of patients required to attempt to answer the question posed. An accepted aspect of clinical research is interim analysis of data accrued on the study. The purpose of interim analysis is to evaluate the data with the object of determining whether the early efficacy and/or toxicity information calls for modification of the study. Occasionally interim analysis will reveal a positive effect which may cause the study to be stopped and reported quickly to the oncologic community. Since a positive study is more exciting and prestigious than a negative study, there is a selective bias toward early publication of studies which appear positive. Unfortunately there is a significant trend in the oncologic literature toward failing to publish the final analysis on a protocol which has been reported years earlier as an interim positive study.

This situation is particularly true in advanced breast cancer where an early emphasis on response rates sometimes gives a study an indication of positivity which is not supported by the ultimate survival data. One of the most often quoted studies in advanced breast cancer is the study by Cooper which reported a 90% complete response rate with a five drug combination. This study was only published as an abstract [1] and was never followed by a full paper. The abstract only spoke about response rate and did not mention survival. Subsequent studies failed to confirm Cooper's report of a 90% complete response rate [2]. In addition, 12 years after the publication of the abstract, there is now serious question about whether the massive number of studies spawned by the abstract have made a significant impact on overall survival in advanced breast cancer.

Chlebowski et al. [3–4], have pointed out the dangers of interim interpretation of breast cancer trials. They have reported on a study of Western Cancer Study Group begun in 1971. In this protocol women with advanced breast cancer were randomized between five-drug combination chemotherapy and sequential use as single agents, of the same five drugs, with treatment changed only after disease progression occurred. The patients were followed to death and survival was the ultimate evaluation of the study.

When the response rate was analyzed early in the study, the combination was superior with an overall response rate of 56% as compared to 32% with the single agents. In March 1974 a survival analysis indicated a significant survival benefit for combination treatment and the study was closed to further case accession. It was reported in the literature as positive study for the combination chemotherapy of breast cancer. After 7 years of follow-up from the initiation of the trial, 90% of the patients entered had expired. A survival analysis at this time, based on more absolute survival data, now failed to show any statistically significant difference between the two arms. Thus the original interpretation of this trial was not supported. As early as March 1975 the significant survival advantage reported for the combination 1 year earlier had disappeared.

Careful analysis of the data reveals several reasons for the early positive result and its failure to remain consistent throughout the analysis. One major reason was that there was a subset of patients that did benefit from the combination regimen. These were patients with hepatic metastases. This subgroup

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of patients died sooner on the single agents regimen and therefore early in the study survival appeared to favor the combination.

A second factor was a reporting delay on five patients on the combination regimen. These patients had actually expired but because of the reporting delay were carried in the March 1974 analysis as still alive. If the death on these patients had been known in March 1974, the survival advantage would no longer have been statistically significant.

The oncologic literature needs more publication of final results. In a disease such as advanced breast cancer, cure is currently not possible and palliation is the goal of therapy. The critical issue for therapeutic decision making will be the survival impact of a regimen within the context of the overall sequential flow of therapies available for use. When nearly all patients have finally expired on a given protocol, then a final report should be made in the literature. This is especially true in situations where the final analysis can be interpreted differently than the results of an earlier published interim analysis. The practicing oncologist should be aware of the bias towards early publication of results that seem positive. Negative results tend to have more maturation of time allowed before publication is attempted. There should also be awareness that actuarial projections of survival are often not totally validated by the absolute survival figures when nearly all patients have died.

References

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