Using Disease-Free Survival as an Alternate Endpoint in Colorectal Cancer Patients

Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005;23:8664–70.

Study Overview

Objective. To assess an alternative endpoint (ie, 3-year disease-free survival [DFS]) for adjuvant colorectal cancer trials.

Design. Retrospective pooled analysis.

Setting and participants. Patient data were collected from 18 randomized phase III adjuvant colon cancer trials with a pooled sample size of 20,898 patients with stage II and III disease. Overall survival (OS) was defined as time from randomization to death from any cause. DFS was defined as time from randomization to first event (either recurrent disease or death.). Follow-up data for all patients were censored at 8 years from randomization. Results with 3 years of median follow-up were reported. A regression model was repeatedly fit using data from all trials.

Main outcome measures. Correlation of 3-year DFS and 5-year OS.

Main results. For years 1 through 5, recurrence rates were 12%, 14%, 8%, 5%, and 3%, respectively. Median time from recurrence to death was 1 year. 80% of recurrences occurred in the first 3 years, and 91% of patients with recurrence by 3 years died before 5 years. Correlation between 3-year DFS and 5-year OS was 0.89. The correlation between hazard ratios for DFS and OS was 0.92 after comparing control and experimental arms in each trial. For 77% of the study arms, the difference between 3-year DFS and 5-year OS was ≤ 3%.

Conclusion. In phase III adjuvant colon clinical trials, DFS and OS are highly correlated within patients and across studies. Three-year DFS is an appropriate endpoint for adjuvant colon cancer clinical trials.

Commentary

Randomized clinical trials are essential for the advancement of treatment in oncology. OS has routinely served as the primary endpoint in phase III oncology trials; however, such randomized trials are never quick and easy. They often require hundreds if not thousands of patients, are costly, and typically take several years for survival data to mature [1,2]. DFS is another common endpoint in oncology clinical trials involving patients with less advanced stages of disease (ie, stages II and III) who are treated with curative intent. Compared with OS, DFS results are achieved sooner and trial sample size requirements are less rigorous. However, historically, DFS has not uniformly predicted OS. The benefits of any treatment in delaying disease recurrence could be confounded by subsequent therapies and not translate to long-term improvement in survival.

In this analysis, Sargent and colleagues hypothesized that DFS can accurately predict OS in patients with colon cancer treated with curative intent and can serve as a preferred endpoint in randomized adjuvant colorectal trials. The authors reviewed results from 18 large phase III trials where patients with nonmetastatic colorectal cancer were randomized to an experimental treatment or control (which could have included more standard chemotherapy). The investigators developed a statistical (regression) model to assess the strength of correlation between DFS and OS for each of these trials and in composite. To some surprise, the authors found that the correlation, while not perfect, was extremely high. This was largely due to the fact that 80% of patient deaths were preceded by recurrence within 8 years of study enrollment, with the majority of recurrences occurring within the first 3 years. Indeed, the study's conclusions are that DFS should be the primary objective of all randomized clinical trials in the adjuvant setting for colorectal cancer.

This study was not a formal meta-analysis of all randomized adjuvant colorectal trials; however, it is strengthened by its inclusion of more than 20,000 patients. The 18 trials varied in terms of treatments (43 different treatment arms), methodology, and included at least 2 studies of rectal cancer. This variation helps reduce potential biases of 1 or more trials in terms of treatment, scheduled follow-up, or patient selection. Importantly, available therapies for patients with recurrent disease during the 1977 to 1999 period over which these studies took place were generally considered to be limited compared with more modern regimens. In the last 5 years, there have been significant improvements in the armamentarium for treating advanced colorectal cancer that poten-

tially could affect this study's conclusions. If, for example, a modern adjuvant trial reported an improved DFS for treatment X over treatment Y, subsequent modern regimens for recurrent disease could level the playing field such that OS is more similar between arms. The authors counter this limitation by pointing out that, even with modern therapies, few patients are living beyond 5 years (a time point considered in this model) and the fundamental relationship between DFS and OS should not change.

Applications for Clinical Practice

Significant improvements in DFS in adjuvant colorectal trials can be considered a strong surrogate for OS.

–Review by David R. Spigel, MD

References

1. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8:431–40.
2. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: Are we being misled? Ann Intern Med 1996;125:605–13.