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Commentary: Clinical Trials Represent the Best Cancer Care. Or Do They?

By Charles D. Blanke

The Mayo clinic Web site states "it's not uncommon for your cancer doctor....to discuss the option of a clinical trial as the *best treatment* [emphasis mine]...for your cancer.¹ In fact, it has long been argued that trial participants have better outcomes than those not enrolled onto such studies.² Many possible explanations for such a phenomenon exist: patients treated on study are likely to be closely monitored (allowing for early dose adjustments, including escalations, as well as

prompt treatment of toxic events); study patients may be more health conscious in general than those not electing to participate; perhaps newer treatments do tend to be better than older standards; and, although it would certainly be hard to definitively prove, it has even been argued clinicians who recruit to trials are in general superior physicians. Of course, reports that attempt to compare trial participants with those treated off-study often attempt to match up different populations with various underlying

imbalances, automatically leading to biases that can skew long-term results.³

In this issue of *Journal of Oncology Practice*, Tanai et al⁴ describe characteristics and outcomes of patients with gastric cancer who declined to participate in a chemotherapy randomized clinical trial (RCT). In brief, The Japan Clinical Oncology Group recently conducted a three-arm, phase III trial testing irinotecan plus cisplatin versus S-1 versus continuous fluorouracil infusion in patients with incurable gastric cancer. Tanai et al actually reviewed medical records of all patients undergoing chemotherapy for advanced stomach cancer between November 2000 and January 2006, and selected 286 patients who were eligible for and had been offered participation in that trial. A variety of information was retrospectively gathered (demographics, performance status, clinical stage, etc), and response and survival outcomes were abstracted. Standard statistical analyses were used in comparing patient characteristics in the groups who participated in the RCT and those who declined, as well as in matching up clinical outcomes. The authors sought to determine whether trial participation itself affected patient outcome, and to confirm whether participants and nonparticipants shared the same characteristics.

Approximately one-third (34%) of patients declined to participate in the RCT. Although FU was recommended to this group, they were allowed to select their own chemotherapy regimen, and approximately 60% elected to take single-agent S-1. The RCT itself reported that combination chemotherapy effected longer survival and that S-1 was noninferior compared with FU. No significant correlations between rate of declining and sex, stage, or performance status were found; younger patients (< 60 years) refused to participate at a much higher frequency. Rates among each of the six physicians offering the trial also differed significantly. There were no major differences in outcome between participants and nonparticipants. Response rate was 9% lower ($P = .121$) and median survival approximately 5% worse for nonparticipants. Interestingly but probably not surprisingly, given the limited treatment options, similar percentages of participants and nonparticipants went on to participate in early-phase experimental trials. The authors concluded patients may have had difficulty in accepting random allocation to study arms expected to have markedly different toxicity (and perhaps efficacy) rates, not to mention different routes of administration for the included drugs.

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They also suggested the rate was affected by who was offering the trial, though this did not correlate with the physicians' years of experience as a GI oncologist. Finally, they concluded outcomes for participants in the RCT were no better.

This article has several limitations, many acknowledged by the authors themselves. All patients accepted treatment of some kind, and the authors had no information on the characteristics of patients who elected best supportive care alone. That group very well might differ from those who accepted active chemotherapy, whether given as part of an RCT or not. Patients included in this article still signed informed consent allowing statistical analysis of their clinical course and outcome; those willing to do so might also differ from patients who refused to participate in a trial of any kind. Numbers were very small, so the numerically different outcomes might have become significant with a larger patient pool, particularly calling into question whether those treated off trial truly do as well as those participating in a study. No data were available regarding the reasons underlying refusal to participate; that information could possibly have been useful in overcoming patient resistance and increasing accrual to future studies. Information garnered might not be generalizable because of the nondiverse patient population, with the situation worsened by the fact the study was limited to a single academic institution.

The authors state their data are exploratory, and they do not make any highly controversial conclusions. However, the interesting questions of whether those participating in a trial are different than the overall nonparticipants with the same disease and whether care on a trial is the best care remain unanswered.

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