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Clinical Trial Results

S0502: A SWOG Phase III Randomized Study of Imatinib, With or Without Bevacizumab, in Patients With Untreated Metastatic or Unresectable Gastrointestinal Stromal Tumors

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Author Summary

Lessons Learned

- Despite having significant rationale, S0502 failed to accrue for a number of reasons.
- Vetting a trial first, with scientific experts and funding agencies, does not guarantee success, especially when dealing with a rare tumor and/or one with an existing highly effective therapy.
- In the present case, adding an intravenous drug to an oral medication as part of a regimen expected to be continued for many years likely decreased patient (and physician) convenience and, thus, interest in the study.

Abstract

Background. Imatinib mesylate, a potent inhibitor of the KIT and PDGFR tyrosine kinases, is highly effective in the treatment of advanced gastrointestinal stromal tumors (GISTs). However, most imatinib-treated tumors eventually become resistant, accounting for a median progression-free survival of 19–23 months. Expression of vascular endothelial growth factor (VEGF) correlates with poor prognosis in GIST; bevacizumab, a monoclonal antibody against VEGF, is effective in a variety of solid tumors. We postulated combination therapy with imatinib plus bevacizumab would benefit patients with advanced GIST, particularly those reliant on VEGFA-dependent angiogenesis.

Methods. Patients with metastatic or surgically unresectable GIST were eligible for this phase III open-label clinical trial, S0502. At registration, patients were randomly assigned to either imatinib 400 mg (standard) or 800 mg (patients with exon 9 *KIT* mutations), or imatinib plus bevacizumab, 7.5 mg/kg i.v. every 3 weeks. Patients were treated to progression, symptomatic deterioration, unacceptable toxicity, treatment delay greater than 4 weeks, or patient choice to withdraw from the study. The primary objective was to determine whether the addition of bevacizumab to imatinib would improve progression-free survival (PFS) in first-line treatment of incurable GIST.

Results. S0502 opened on April 15, 2008. As of fall 2009, only 12 patients from at least 178 eligible SWOG centers plus those participating through Cancer Trials Support Unit had been entered in the study. Despite an aggressive promotion scheme involving the other cooperative groups and a major GIST patient advocacy group, accrual remained slow. The trial was closed on October 1, 2009, having accrued only 2% of the 572 patients planned. No scientific conclusions were forthcoming because of the small number of patients entered in the study. Two patients of the 6 in the combination arm reported grade 3 toxicities, 1 with proteinuria and 1 with fatigue, upper gastrointestinal hemorrhage, and anemia.

Conclusion. No conclusions may be drawn from this trial and, thus, the combination of imatinib plus bevacizumab cannot be recommended for use. ***The Oncologist*** 2015;20:1353–1354

Discussion

Despite the overwhelming success of imatinib in prolonging PFS of treated patients with advanced GIST, the drug is not curative. After imatinib mesylate became standard-of-care

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therapy for advanced disease, very few up-front trials have been done. Targeting angiogenesis appeared quite reasonable based on the correlation of VEGF expression with poor outcome in GIST, as well as the potential anti-VEGF receptor action of sunitinib and regorafenib, other drugs approved for the treatment of tumors deemed resistant to imatinib.

Although the idea of combining imatinib and bevacizumab was widely circulated among international GIST experts and enthusiastically vetted at the highest levels before the study opened, intergroup participation in S0502 remained poor from the start. Multiple attempts to increase patient participation, including loosening the eligibility criteria (to allow brief prior imatinib therapy in the advanced setting), principal investigator talks with all the North American cooperative groups, and extensive discussions and website advertising with the Life Raft Group, a GIST patient advocacy organization, failed to improve the situation. Some factors implicated in early closure of other phase III studies did not contribute. For example, S0502 did not close because of a change in standard of care; imatinib has been the accepted frontline treatment from 2001 until the present. Similarly, there were no competing trials in the cooperative groups, and the trial did not lose its funding. Other potential causes for early closure, some common to other trials and some relatively unique, should be entertained. Imatinib itself induces an extraordinarily high response rate and is now associated with overall survival of approximately 5 years or more. It is possible community medical oncologists treating GIST felt imatinib alone could never be improved upon and, thus, did not want to go through the added work of opening the protocol or accruing patients. Clearly, adding an intravenous drug to an oral medication decreased patient (and physician) convenience and, thus, interest in the study.

Phase III trials, in general, often fail to meet their accrual goals; Cheng et al. have suggested this occurs with as many as 71% of studies [1]. In a retrospective review of all National Cancer Institute Cancer Therapy Evaluation Program-sponsored therapeutic trials (June 2000 to December 2004) with complete tracking information regarding development time, Cheng et al. discovered studies taking longer than 24 months to develop and open were significantly less likely to succeed (odds ratio: 0.4) [1]. As evidenced by the fact that planning for S0502 began in 2005, coupled with the 2008 opening, S0502 missed even that mark substantially. Finally, no phase II study testing the regimen was performed; while it would have been difficult to achieve a marker of potentially improved efficacy from such a study, a secondary objective, such as feasibility or even accrual rate, might have given a signal to proceed (or not) with a larger, randomized, phase III trial. No meaningful results emerged from 0502. The slow accrual and lack of meaningful results for S0502 remain quite disappointing, as does the likelihood that the potential use and importance of angiogenesis as a therapeutic target in GIST will never be effectively studied.

Author disclosures and references available online.