Overview

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Title: 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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Disclosures

Christopher Corless: Novartis, Genentech (C/A, H); **Karen Mulder:** Leo Pharma. Inc., Sanofi Canada (C/A), Bayer, Amgen, Roche (RF); **Suzanne George:** Novartis, Pfizer, Bayer, Ariad (RF); **Michael Heinrich:** Novartis, Pfizer, Ariad, Blueprint, MolecularMD (C/A), Novartis, Ariad, Blueprint (RF), Novartis (ET), Pfizer, Novartis (H), MolecularMD (OI), patents related to PDGFRA (IP). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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.

Author Summary: Abstract and Brief Discussion

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.

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 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.

Trial Information

Disease	Gastrointestinal Stromal Tumor
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase III
Type of study - 2	Randomized
ORR	P:, HR:
PFS	P:, HR:
TTP	P:, HR:
Response Duration	P:, HR:
Primary Endpoint	Progression-Free Survival
Secondary Endpoint	Overall Response Rate
Secondary Endpoint	Correlative Endpoint
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	Correlative work included exploring soluble VEGF and receptors, Ang-2, *KIT* and *PDGFR* mutations, and single nucleotide polymorphisms in *ABCG2* and *CYP3A4*, as well as a preliminary evaluation of a metabolic-based non-RECIST imaging response assessment system.
Investigator's Analysis	Unable to assess

Drug Information Control Arm

Drug 1 **Generic/Working name**	Imatinib mesylate
Trade name	Gleevec
Company name	Novartis
Dose	400 mg (standard), 800 mg (patients with exon 9 *KIT* mutations) per flat dose
Route	Oral
Schedule of Administration	Daily

Drug Information Experimental Arm

Drug 1 **Generic/Working name**	Imatinib mesylate
Trade name	Gleevec
Company name	Novartis
Dose	400 mg (standard), 800 mg (patients with exon 9 *KIT* mutations) per flat dose
Route	Oral
Schedule of Administration	Daily
Drug 2 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Genetech
Drug type	Biological
Drug class	Angiogenesis
Dose	15 mg/kg
Route	i.v.
Schedule of Administration	Every 21 days

Patient Characteristics

Number of patients, male	4
Number of patients, female	8
Stage	Not Collected
Age	Median (range): control arm, 57.9 years (44.0–68.5 years); experimental arm, 64.7 years (49.4–82.9 years)
Number of prior systemic therapies	Median (range): Not Collected
Performance Status: ECOG	0 — 9 1 — 2 — 3 — Unknown —
Other	3 patients with performance status ≥1

Primary Assessment Method

Control Arm: Total Patient Population

Number of patients enrolled	6
Number of patients evaluable for toxicity	6
Number of patients evaluated for efficacy	3
Evaluation method	CT/MRI. Same assessment used at baseline must be used for response assessment.

Experimental Arm: Total Patient Population

Number of patients enrolled	6
Number of patients evaluable for toxicity	6
Number of patients evaluated for efficacy	0
Evaluation method	CT/MRI. Same assessment used at baseline must be used for response assessment.

Adverse Events Control Arm

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue (asthenia, lethargy, malaise)	84%	16%	0%	0%	0%	0%	16%
Hypertension	84%	16%	0%	0%	0%	0%	16%
Blood/Bone Marrow - Leukopenia	84%	0%	16%	0%	0%	0%	16%
Mucositis/stomatitis (functional/symptomatic)	84%	0%	16%	0%	0%	0%	16%
Nausea	68%	16%	16%	0%	0%	0%	32%
Metabolic/Laboratory - Transaminitis	84%	16%	0%	0%	0%	0%	16%
Hemorrhage/Bleeding - GI	84%	16%	0%	0%	0%	0%	16%
Edema: head and neck	84%	16%	0%	0%	0%	0%	16%
INR (International Normalized Ratio of prothrombin time)	84%	0%	0%	16%	0%	0%	16%
Thrombosis/embolism (vascular access related)	84%	0%	0%	16%	0%	0%	16%
Vomiting	67%	33%	0%	0%	0%	0%	33%
Hemoglobin	67%	33%	0%	0%	0%	0%	33%
Constipation	84%	0%	16%	0%	0%	0%	16%

Adverse Events Legend
*No Change from Baseline/No Adverse Event

Adverse Events Experimental Arm

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Anorexia	84%	0%	16%	0%	0%	0%	16%
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	84%	16%	0%	0%	0%	0%	16%
Cough	84%	16%	0%	0%	0%	0%	16%
Creatinine	84%	0%	16%	0%	0%	0%	16%
Diarrhea	68%	16%	16%	0%	0%	0%	32%
Distension/bloating, abdominal	84%	16%	0%	0%	0%	0%	16%
Dyspnea (shortness of breath)	84%	16%	0%	0%	0%	0%	16%
Edema: limb	84%	0%	16%	0%	0%	0%	16%
Hemoglobin	68%	16%	0%	16%	0%	0%	32%
Albumin, serum-low (hypoalbuminemia)	84%	0%	16%	0%	0%	0%	16%
Calcium, serum-low (hypocalcemia)	84%	0%	16%	0%	0%	0%	16%
Insomnia	84%	16%	0%	0%	0%	0%	16%
Hemorrhage/Bleeding - Other (Lung hemorrhage, nose)	84%	16%	0%	0%	0%	0%	16%
Fatigue (asthenia, lethargy, malaise)	68%	16%	0%	16%	0%	0%	32%
Hypertension	84%	0%	16%	0%	0%	0%	16%
Constipation	84%	0%	16%	0%	0%	0%	16%

Adverse Events Legend
*No Change from Baseline/No Adverse Event

Serious Adverse Events Experimental Arm

Name	Grade	Attribution
Upper GI hemorrhage	3	Probable
Proteinuria	3	Definite

Serious Adverse Events Legend
Two patients of the 6 on the combination arm reported grade 3 toxicities, 1 with proteinuria and 1 with fatigue, upper GI hemorrhage, and anemia.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Did not fully accrue
Investigator's Assessment	Unable to assess

Discussion

Despite the overwhelming success of imatinib in prolonging progression-free survival (PFS) of treated patients with advanced gastrointestinal stromal tumor (GIST), the drug is not curative. Many drugs are being tested in patients who have failed imatinib, sunitinib, and regorafenib; after imatinib mesylate became standard-of-care therapy for advanced disease, very few up-front trials have been done. The need to identify new targets and develop new drugs in patients with untreated GIST remains real. Targeting angiogenesis appeared quite reasonable based on the correlation of vascular endothelial growth factor (VEGF) expression with poor outcome in GIST, as well as the potential anti-VEGF receptor action of sunitinib—the latter evidenced by activity in patients with imatinib-resistant tumors and the relatively improved response rates of GISTs not driven by *KIT* mutations (sporadic wild-type, pediatric) to that drug.

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 front-line treatment from 2001 until 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.

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No meaningful results emerged from S0502. Even the most rudimentary analysis shows the same number of patients, or fewer, remained on treatment long term, thus not allowing even the suggestion that combination therapy might have been superior to single-agent imatinib. 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.

Reference

1. Cheng SK, Dietrich MS, Dilts DM. A sense of urgency: Evaluating the link between clinical trial development time and the accrual performance of cancer therapy evaluation program (NCI-CTEP) sponsored studies. Clin Cancer Res 2010;16:5557–5563.

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