Sunitinib malate for gastrointestinal stromal tumour in imatinib mesylate–resistant patients: recommendations and evidence

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ABSTRACT

Question

Is sunitinib malate—marketed as Sutent (Pfizer Canada, Kirkland, QC)—superior to placebo or other interventions for primary outcomes of interest in adult patients with gastrointestinal stromal tumour (GIST) who have developed resistance or who exhibit intolerance to imatinib mesylate (IM)?

Background

In patients with resectable disease, surgery is the mainstay of treatment for GIST; in patients with unresectable or metastatic disease, the tyrosine kinase inhibitor IM is the therapy of choice. However, some patients have primary resistance or intolerance to IM, or they progress after optimal exposure (including an escalated dose). Here, we review the evidence for treating IM-resistant GIST with sunitinib malate.

Methods

Studies of sunitinib malate were identified through MEDLINE, EMBASE, the Cochrane Library databases, and Web sites of guideline organizations. Outcomes of interest included time to progression, progression-free survival, overall survival, and toxicity.

Results

One phase III randomized controlled trial, and one abstract and presentation describing that trial, served as the evidentiary base for this clinical practice guideline. Trial data confidently show that both time to progression and progression-free survival are highly statistically significant ($p < 0.0001$) in favour of sunitinib malate over placebo. Overall survival was improved with sunitinib malate (hazard ratio: 0.49; 95% confidence interval: 0.29 to 0.83; $p = 0.007$; absolute difference in weeks not reported). The most frequent of all adverse effects (experienced in greater proportion by patients on sunitinib malate) were grades 1 and 2 leucopenia (52% vs. 5% with placebo), neutropenia (43% vs. 4%), and thrombocytopenia (36% vs. 4%). Grade 3 hematologic adverse events were also reported more frequently in the sunitinib malate group, including leucopenia (4% vs. 0%), neutropenia (8% vs. 4%), lymphopenia (9% vs. 2%), and thrombocytopenia (4% vs. 0%). Toxicity comparisons did not include p values.

The incidence of grades 1–3 fatigue was greater for the sunitinib malate group (34% vs. 22% with placebo). Other grade 3 nonhematologic treatment-related adverse events that occurred more frequently on sunitinib malate included hand–foot syndrome (4% vs. 0%), diarrhea (3% vs. 0%), and hypertension (3% vs. 0%). No grade 4 adverse events were observed.

Conclusions

In the target population, sunitinib malate is the recommended option for second-line therapy of metastatic GIST.

KEY WORDS

Sarcoma, sunitinib malate, gastrointestinal stromal tumour, GIST, imatinib mesylate resistance

1. QUESTION

Is sunitinib malate—marketed as Sutent (Pfizer Canada, Kirkland, QC)—superior to placebo or other interventions for primary outcomes of interest in adult patients with gastrointestinal stromal tumour (GIST) who have developed resistance or who exhibit intolerance to imatinib mesylate (IM)?

2. CHOICE OF TOPIC AND RATIONALE

A rare mesenchymal tumour, GIST is characterized by unique histologic and immunohistochemical features, including overexpression of the C-kit receptor. In patients with resectable disease, surgery is the mainstay of treatment. However, in patients with unresectable or metastatic disease, therapy with the tyrosine kinase inhibitor (TKI) IM, marketed as Gleevec (Novartis Pharmaceuticals, St. Louis, MO, U.S.A.), is the therapy of choice. The Sarcoma Disease Site Group (DSG) previously reviewed the efficacy and toxicity of IM in that setting [1].

Although IM has irrevocably altered the course of GIST, with a significant improvement in time to progression and median overall survival, comparison with historical data shows that it is by no means a curative therapy and that most patients eventually progress. In such circumstances, patients who have demonstrated a prior response to IM at the usual starting dose of 400 mg daily are escalated to 800 mg daily, because up to one third may exhibit stable disease through such a strategy. However, in patients who progress on initial therapy with IM (approximately 15%) or in those who progress after dose escalation, therapeutic options are extremely limited.

The success of IM has provoked the development of an array of TKIS, of which sunitinib malate (marketed as Sutent) is the most advanced in clinical trials. Sunitinib malate is an oral agent that inhibits phosphorylation of multiple tyrosine kinases, including C-kit, platelet-derived growth factor receptor, and vascular endothelial growth factor receptor. As such, it is a logical agent to study in GIST. Because of the high efficacy of IM in GIST, it was thought to be medically and ethically appropriate to study sunitinib malate in patients who had primary resistance or intolerance to IM or in those who had progressed after optimal exposure to IM (including an escalated dose). The Sarcoma DSG therefore undertook a review of the evidence.

3. METHODS

3.1 Guideline Development

This evidence-based series produced by the Program in Evidence-Based Care (PEBC) is a convenient and up-to-date source of the best available evidence on the role of sunitinib malate in GIST. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members (JY, SV) of the PEBC Sarcoma DSG and by two methodologists (JF, NC).

The body of evidence in this review is composed entirely of one published phase III randomized controlled trial (RCT) and related abstracts presented at the 2003–2006 American Clinical Society of Oncology (ASCO) annual meetings.

3.2 Literature Search Strategy

The MEDLINE (1996 through April 14, 2008) and EMBASE (1996 through April 14, 2008) databases and the Cochrane Central Register of Controlled Trials (CENTRAL, 1996 through April 14, 2008) were searched for relevant articles. Search terms included treatment-specific terms such as "sunitinib malate," "Sutent," or "SU11248," combined with disease-specific terms such as "GIST" or "gastrointestinal stromal tumour" (Table I).

In addition, the 2003–2008 conference proceedings of the ASCO annual meetings were searched for abstracts of relevant trials. The Canadian Medical Association InfoBase, the U.S. National Guideline Clearinghouse, and the U.K. National Institute for Health and Clinical Excellence were also searched for existing evidenced-based guidelines.

3.3 Study Selection Criteria

Articles were eligible for inclusion if they

- evaluated sunitinib malate as treatment for adult patients (≥15 years of age) with GIST in a phase III RCT,
- were published as full peer-reviewed articles or publicly-available abstracts or presentations, and
- reported data on one or more of the following outcomes: objective response rate, time to progression, stable disease rate, progression-free survival, overall survival, toxicity, or quality of life.

Articles were excluded if they were nonrandomized phase I or II clinical trials, retrospective studies, editorials, letters, or articles. Articles published in languages other than English were also excluded because translation capacity was not available.

4. LITERATURE SEARCH RESULTS

The literature search identified one phase III RCT by Demetri *et al.* in full publication [2]. No existing practice guidelines or systematic reviews were found. Four abstracts were identified that described the phase III RCT by Demetri *et al.* [3–6]. Those abstracts were presented at the ASCO 2005 [4] and 2006 [3,5] annual meetings and at the ASCO 2006 Gastrointestinal Cancers Symposium [6]. Three accompanying presentations were also identified [3,4,6]. Only one of the abstracts [3] (and its accompanying presentation) updated trial results beyond the original full-publication trial reports of the study [2]. The other abstracts [4–6] presented inutile or redundant data and thus are not further reported or discussed here.

The double-blind RCT by Demetri *et al.* [2] examined the use of sunitinib malate in the target population. Results reported here (Table II) were derived

TABLE I Search strategy

Step	*MEDLINE*	*EMBASE*
1	exp Gastrointestinal Stromal Tumors/	exp Gastrointestinal Stromal Tumor/
2	GIST.tw.	GIST.tw.
3	sunitinib malate.tw.	sunitinib malate.tw.
4	Sutent.tw.	sunitinib?.tw.
5	SU11248.tw.	Sutent.tw.
6	randomi?ed controlled trial.pt.	SU11248.tw.
7	exp Randomized Controlled Trials/	Randomized Controlled Trial/
8	phase II.tw.	randomi?ed.tw.
9	exp clinical trials, phase ii/ or exp clinical trials, phase iii/	Phase 2 Clinical Trial/
10	phase III.tw.	Phase 3 Clinical Trial/
11	1 or 2	phase II.tw.
12	sunitinib?.tw.	phase III.tw.
13	or/3–5	1 or 2
14	12 or 13	or/3–6
15	6 or 7	7 or 8
16	or/8–10	or/9–12
17	11 and 14	15 or 16
18	15 or 16	13 and 14
19	17 and 18	17 and 18

TABLE II Efficacy results for sunitinib malate in patients with gastrointestinal stromal tumour who have developed resistance or who exhibit intolerance to imatinib mesylate

Efficacy parameter	*Sunitinib (n=207)*	*Placebo (n=105)*	*p Value (log-rank test)*	*HR*	*95% CI*
Median TTP [weeks (months)]	27.3 (6.4)	6.4 (1.5)	<0.0001	0.33	0.23 to 0.47
95% CI	16.0 to 32.1	4.4 to 10.0			
Median PFS [weeks (months)]	24.1 (5.6)	6.0 (1.4)	<0.0001	0.33	0.24 to 0.47
95% CI	11.1 to 28.3	4.4 to 9.9			
Partial response (%)	6.8	0			
Durable stable disease (%)	17.4	1.9			
Objective response rate (%)	7	0	0.006		
95% CI	3.7 to 11.1	—			

HR = hazard ratio; CI = confidence interval; TTP = time to tumour progression; PFS = progression-free survival.

at the time of a first (planned) interim analysis. In 312 patients randomized 2:1 (207 sunitinib malate, 105 placebo), median time to progression (primary endpoint) was significantly longer in patients treated with sunitinib malate [27.3 weeks vs. 6.4 weeks; hazard ratio (HR): 0.33; 95% confidence interval (CI): 0.23 to 0.47; $p < 0.0001$]. Similar HRs in favour of sunitinib malate were reported in stratified analyses and in Cox proportional hazard models that controlled for baseline factors. Patients treated with sunitinib malate had longer progression-free survival (24.1 weeks vs. 6.0 weeks; HR: 0.33; 95% CI: 0.24 to 0.47; $p < 0.001$) and improved overall survival (HR: 0.49; 95% CI: 0.29 to 0.83; $p = 0.007$; absolute difference in weeks not reported) [2].

Sunitinib malate therapy induced a partial response in 6.8% of patients (vs. 0% with placebo) and durable stable disease (stable disease ≥ 22 weeks, deemed clinically significant) in 17.4% (vs. 1.9% with placebo) [3]. The objective response rate was significantly higher in patients treated with sunitinib malate (7.0% vs. 0%; 95% CI: 3.7 to 11.1%; $p = 0.006$) [2]. Of

9 IM-resistant patients, 4 achieved a partial response with sunitinib malate therapy; 0 of 4 IM-resistant patients achieved partial response with placebo [3].

Over time, quality of life between the sunitinib malate and placebo arms of the trial was not different, as measured by the EuroQOL visual analog scale. A nonsignificant trend toward a higher pain-relief response rate was observed for sunitinib malate over placebo in the intention-to-treat population (17.4% vs. 9.5%, $p = 0.064$) and in patients who reported pain or analgesic use at baseline (31.0% vs. 17.2%, $p = 0.052$) [3].

Sunitinib malate therapy was generally well tolerated (Table III). The most frequent of all adverse effects (experienced in greater proportion by patients on sunitinib malate) were grades 1 and 2 leucopenia (52% vs. 5% with placebo), neutropenia (43% vs. 4%), and thrombocytopenia (36% vs. 4%). Grade 3 hematologic adverse events were also reported more frequently in the sunitinib malate group, including leucopenia (4% vs. 0% with placebo), neutropenia (8% vs. 4%), lymphopenia (9% vs. 2%), and thrombocytopenia (4% vs. 0%). Toxicity comparisons did not include *p* values.

Among nonhematologic adverse events, grades 1–3 fatigue were more common in the sunitinib malate group (34% vs. 22% with placebo). Other grade 3 nonhematologic treatment-related adverse events that occurred more frequently with sunitinib malate included hand–foot syndrome (4% vs. 0% with placebo), diarrhea (3% vs. 0%), and hypertension (3% vs. 0%). No grade 4 adverse events were observed.

Patients who were intolerant to IM on study entry did not experience a recurrence of previous toxic effects when on sunitinib malate. No patients had clinical evidence of congestive heart failure, pancreatitis, or a mean decrease in left ventricular ejection fraction [2].

TABLE III Adverse events for sunitinib malate in patients with gastrointestinal stromal tumour who have developed resistance or who exhibit intolerance to imatinib mesylate

Adverse effects	*Sunitinib (n=202)*	*Placebo (n=102)*
Grade 1/2 adverse effects (%)		
Leucopenia	52	5
Neutropenia	43	4
Thrombocytopenia	36	6
Grade 3 hematologic adverse events (%)		
Leucopenia	4	0
Neutropenia	8	4
Lymphopenia	9	2
Thrombocytopenia	4	0
Grade 3 non-hematologic adverse events (%)		
Grade 1–3 fatigue	34	22
Hand–foot syndrome	4	0
Diarrhea	3	0
Hypertension	3	0

5. DSG CONSENSUS PROCESS

The draft guideline was circulated to the Sarcoma DSG for review and discussion. The group approved the document and agreed that no major changes were necessary.

6. REVIEW AND APPROVAL BY THE PEBC REPORT APPROVAL PANEL

The final report was also reviewed and approved by the PEBC report approval panel, which consists of 2 members, including an oncologist with expertise in clinical and methodologic issues. Key issues raised by the report approval panel included the need for an *a priori* statement identifying outcomes of interest and for discussion regarding the choice of placebo as comparator and how the IM resistance and intolerance criteria were derived. They also identified a need to discuss the methodologic importance of stopping clinical trials early in the presence of benefit and noted that some of the secondary outcomes should be separated into their own paragraphs, apart from the key evidence. They further indicated that the implications of sunitinib malate as first-line therapy should be discussed.

The Sarcoma DSG received and responded to all comments. A discussion section was added to address most of the concerns and to provide additional context and commentary. Key evidence was separated from secondary evidence to highlight the outcomes of interest that are considered most important in terms of driving policy, and an "Outcomes of Interest" heading was added. Lastly, given that no trials have reviewed sunitinib malate as first-line therapy for metastatic GIST, the Sarcoma DSG felt unable to comment (outside of pure speculation) on the use sunitinib malate in that way, and thus no discussion about that topic was included.

7. EXTERNAL REVIEW

7.1 Methods

The Sarcoma DSG circulated the draft clinical practice guideline and systematic review to practitioners in Ontario for review and feedback. The PEBC external review process is two-pronged and includes

- a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and
- a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

7.2 Targeted Peer Review

During the guideline development process, the Sarcoma DSG identified 6 targeted peer reviewers from Ontario, Quebec, Manitoba, and British Columbia considered to be clinical or methodology experts on the topic. Several weeks before completion of the draft report, the nominees were contacted by e-mail and asked to serve as reviewers. Two reviewers agreed, and the draft report and a questionnaire were sent by e-mail for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent on February 24, 2009 . Follow-up reminders were sent at 2 weeks (e-mail) and at 4 weeks (telephone call). The Sarcoma DSG reviewed the results of the survey.

The two reviewers rated the guideline to be of high quality on methods, presentation, recommendations, completeness of reporting, information included, and quality. Both reviewers said that they would use the guideline in their practice. There were no barriers reported to the implementation of the report.

7.3 Summary of Written Comments and Modifications or Actions

The reviewers made several suggestions. One comment was about the dosing recommendations in the context of disease progression and resistance to IM. In response, the wording of the guideline recommendations was changed to improve clarity. One reviewer suggested including the importance of FLT3 inhibition because it explains some of the toxicities and is the reason behind the unusual dosing schedule. The DSG acknowledges that this is an area of further research, but no changes were made in the document. Finally, a reviewer thought that daily dosing with sunitinib is successfully skirted because of the methodology used. The Sarcoma DSG is recommending the clinical trial dosage, and so no changes were made in the document.

7.4 Professional Consultation

Feedback was obtained through a brief online survey of the health care professionals who are the intended users of the guideline. All medical oncologists in the PEBC database who treat sarcoma were contacted by e-mail about the availability of the survey. They were directed to the survey website, where they were provided with access to the survey, the guideline recommendations, and the evidentiary base. Participants were asked to rate the overall quality of the guideline and whether they would use and recommend it. Written comments were invited. The notification e-mail was sent on March 12, 2009. The consultation period ended on April 30, 2009. The Sarcoma DSG reviewed the results of the survey. No responses were received, and no action was taken.

8. PRACTICE GUIDELINE

8.1 Recommendations

Sunitinib malate administered at a dose of 50 mg daily in 6-week cycles (4 weeks on, 2 weeks off) is a recommended treatment option in patients with unresectable or metastatic or recurrent GIST who demonstrate

- early progression at any time during the first 6 months while on optimum doses of IM [as measured by the Response Evaluation Criteria in Solid Tumors (RECIST)].
- progression after treatment with IM in doses of 400–1600 mg daily for an appropriate duration (as measured by RECIST)[a].
- intolerance to IM.

Treatment should continue in 6-week cycles until progression or intolerance. Patients should be encouraged to participate in appropriate clinical trials.

8.2 Qualifying Statements

This review addresses the results of a single trial presented across several publications. The trial was stopped early after a planned interim analysis. Subjects were unblinded and allowed to cross over to sunitinib malate from placebo. Notwithstanding the ethical considerations that should be taken into account in such settings, there is growing concern in the literature over trials that are stopped prematurely, and clinicians should interpret results of this sunitinib malate trial only after understanding the methodologic concerns (see the Discussion section).

Resistance to IM was defined by progression as denoted by RECIST. Thresholds for progression as bulleted in the recommendations—for example, early progression (within 6 months) while on IM, and progression after treatment with escalated doses of IM (up to 1600 mg)—were established both according to the entry criteria of the trial under review and based on prior knowledge and standard practice for using IM in recurrent or metastatic GIST (see the Discussion section).

In the original trial report by Demetri *et al.* [2],

- at the time of documented disease progression, treatment assignments were unblinded. Placebo patients were given the option of switching to sunitinib malate, and patients who were already

[a] Because of toxicity concerns, the Sarcoma DSG does not advise escalating doses of IM beyond 800 mg daily.

receiving sunitinib malate were given the opportunity to continue treatment at the investigator's discretion. As a result, and when considering the short follow-up, the differences in overall survival between treatment groups may have been reduced at the time of the first (planned) interim analysis.
- study populations were analyzed according to intention-to-treat (all patients as randomized according to original randomization scheme), modified intention-to-treat (all intention-to-treat patients with disease progression on IM), and per protocol (all patients who received at least 1 dose of the assigned study treatment). Intention-to-treat data were reported for all efficacy measures and per protocol for safety.

In the updated presentation at the 2006 ASCO annual meeting [3],

- analyses included placebo patients who had crossed over to sunitinib malate treatment after the observation of favourable results for median time to progression at the time of the first (planned) interim analysis (as noted earlier). Thus, any updated analyses reflect immediate versus delayed sunitinib malate treatment and not sunitinib malate versus placebo as reported for the original trial.
- the progression analyses in the delayed-treatment arm included only those patients originally randomized to placebo who crossed over to receive sunitinib malate treatment before any disease progression (hence the low sample size: $n = 24$).
- because the placebo patient crossover altered the planned trial methodology, no statistical adjustments for the earlier interim analyses were necessary for the updated data.

9. DISCUSSION

In patients with unresectable or metastatic GIST, therapy with IM at an initial dose of 400 mg daily is the recommended standard of care [1]. Complete responses with IM are rare; most patients exhibit partial responses, with progression observed after a median of 2 years. In such patients, the recommendation is that IM be escalated to 800 mg daily. Furthermore, patients who progress early (≤6 months) on conventional-dose IM (400 mg daily) do not derive any benefit from dose escalation and thus have limited therapeutic options [1]. For those patients, or for others progressing at any point along the treatment continuum, salvage therapies are available, including surgery or radioablation for areas of localized progression. Because such therapies have not been consistently or prospectively evaluated, it is difficult to comment with confidence on their benefit. As a consequence, no widely accepted or standard second-line (post-IM) therapeutic options have been available until now.

The study of sunitinib malate versus placebo by Demitri *et al.* [2] is the only RCT of a TKI in the second-line setting for patients with advanced GIST. Trial data confidently show that time to progression and progression-free survival are both highly statistically significant ($p < 0.0001$) in favour of sunitinib malate. Sunitinib malate is therefore a recommended option for the second-line therapy of metastatic GIST in the target population. But despite the promising results, some important methodologic concerns must be addressed when interpreting the results of this study.

The choice of a placebo as the comparator might be considered inappropriate, possibly biasing results in favour of sunitinib malate. However, in the absence of any other widely applied second-line approach, including best supportive care, and in light of concerns over the potential side effects (harms) of escalated IM (>800 mg daily) or of cascading multiple-TKIs for all patients, a placebo-controlled trial would appear to be the optimal design.

There is also concern about the early stoppage of this trial after the interim analysis observed benefit. Early termination of clinical trials because of benefit often overestimates overall treatment effect because such trials tend to be on a "random high" with subsequent follow-up data from the same or similar trials showing "regression to the truth" [7–10]. However, the early termination in this trial is unlikely to invalidate the finding of benefit for sunitinib malate. First, an Independent Data and Safety Monitoring Board, a staple in modern clinical trials, was used to decide termination. Second, the trial managed to achieve its target sample size, and the termination event number was still beyond 50% of the planned number, thus reducing the risk of stopping on a "random high"—a phenomenon often attributable to smaller termination-sample sizes. Third, no predefined statistical termination boundary was reported, but the large effect size for the primary endpoint (a time to progression more than 4 times longer for sunitinib malate than for placebo) and the associated small p value (<0.0001) satisfies even the most stringent of interim stoppage boundary rules in today's literature (for example, the Haybittle–Peto boundary). Fourth, after placebo-patient crossover, this trial continued to accrue data and showed a further trend toward both time-to-progression and survival benefit for delayed sunitinib malate. This dose-like relationship adds confidence to the interim findings of a clinical benefit for sunitinib malate.

A final concern is whether the trial population was representative of the clinical world. Although the median maximal dose of IM was 800 mg daily, an unknown number of patients experienced dose escalation of IM up to 1600 mg daily [2]—a dose that is rarely used in day-to-day practice. The effects that this dose escalation would have had, if any, on the

overall efficacy or safety of sunitinib malate in the trial under review are unclear. However, it is possible that patients receiving upwards of 1600 mg daily of IM were in a late stage of disease and thus less likely to derive benefit from sunitinib malate, *lowering* the therapeutic effect size for the sunitinib malate.

The idea that patients can be switched to sunitinib malate early during the course of their disease is supported by the observation that, during subgroup analysis, a significant time-to-progression benefit was found in patients exhibiting primary resistance to IM (progressive disease within 6 months of IM therapy, 17% of the total trial population) [2]. Future trials with a more representative patient population may thus find a greater benefit if sunitinib malate is offered to patients early in the course of disease progression in place of an escalation in the maximum dose of IM beyond 800 mg daily, which is not recommended because of toxicity concerns [1].

10. POLICY REVIEW

A report on sunitinib for GIST was sent to the Committee to Evaluate Drugs in October 2007.

11. PRACTICE GUIDELINE DATE

This guideline was completed in June 2009. Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit the Cancer Care Ontario Web site (www.cancercare.on.ca) for the full evidence-based series report and subsequent updates.

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§ Please see the page for the Sarcoma Disease Site Group (www.cancercare.on.ca/cms/one.aspx?pageId=10355 at June 2010) in the Program in Evidence-Based Care section of the Cancer Care Ontario Web site for a complete list of current group members.