A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Evidence-based Series 11-7 Version 3 ARCHIVED 2019

Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours

Members of the Sarcoma Disease Site Group

An assessment conducted in March 2019 ARCHIVED Evidence-based Series (EBS) 11-7 Version 3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document.
(PEBC Assessment & Review Protocol)

EBS 11-7 Version 3 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1181

1. **Guideline Report Overview**
2. **Section 1: Clinical Practice Guideline**
3. **Section 2: Systematic Review**
4. **Section 3: Guideline Development and External Review**
5. **Document Assessment and Review Tool**

Release Date: May 31, 2015

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version April 2006	1996 to 2005	Full Report	Web publication	NA
Version 2 Sep 2011	2006 to 2011	New data found in Document Assessment and Review Tool	Updated Web publication	Original Guideline Recommendations ENDORSED
Version 3 Jan 2015	2006-2011	New evidence was added to Section 1 to support the diagnostic criteria evolving in recent years.	Updated Web Publication	Original Guideline Recommendations ENDORSED

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Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours

Guideline Review Summary

Review Date: May 31, 2011

The 2006 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2006. In May 2011, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Practice Guideline and Systematic Review in this version are the same as in the April 2006 version.

With the diagnostic criteria for GIST evolving in the recent years, the PEBC and the Sarcoma DSG added key evidence (found in section 1).

Update Strategy

Using the Document Assessment and Review Tool at the end of this report, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

Does treatment with imatinib mesylate (Gleevec™) have palliative benefit, in terms of tumour response, disease progression, survival or quality of life, for patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining)?

Literature Search and New Evidence

The new search (2006 to March 2011) yielded six relevant new publications from one meta-analysis and four randomized controlled trials (RCTs). One RCT was already included in the existing guideline. Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations for EBS 11-7 (imatinib mesylate in adult patients with unresectable or metastatic GIST). Hence, the Sarcoma DSG **ENDORSED** the 2006 recommendations on imatinib mesylate in adult patients with unresectable or metastatic GIST.

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Evidence-based Series 11-7: Section 1

Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours: A Clinical Practice Guideline

S. Verma, J. Younus, D. Stys-Norman, A.E. Haynes, M. Blackstein,
and the Sarcoma Disease Site Group

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Please see the EBS 11-7 Guideline Review Summary and the Document Assessment and Review Tool for summary of updated evidence published between 2006 and 2011.

Report Date: April 6, 2006

Question

Does treatment with imatinib mesylate (Gleevec™) have palliative benefit, in terms of tumour response, disease progression, survival or quality of life, for patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining)?

Target Population

These recommendations apply to adult patients with unresectable or metastatic GIST expressing KIT (CD117+).

Recommendations

- In patients with KIT-expressing (CD117+) unresectable or metastatic GIST, treatment with imatinib is a recommended therapy.
- Until additional data become available, the initial dose of imatinib should be prescribed at a dose of 400 mg daily. A dose of 400 mg twice daily may be considered in patients who demonstrate progression on the lower dose.

- The optimal duration of therapy in responding patients or in those patients who achieve a complete clinical and/or radiologic remission has not yet been defined. Phase III trials have demonstrated benefit for up to two years of continued therapy.
- Eligible patients with GIST who do not respond adequately to optimum doses of imatinib should be considered for entry into a clinical trial.

Qualifying Statements

- It is acknowledged that there are no randomized controlled trials (RCTs) comparing imatinib to no treatment or best supportive care thereby making it difficult to statistically quantify the benefits for progression free survival and overall survival conferred by imatinib. The Sarcoma DSG has concluded that such trials will never be performed in the future in patients with unresectable or metastatic GISTs. In framing its recommendations, the DSG has also borne in mind the fact that treatment with imatinib in such patients has already gained wide acceptance among oncologists internationally.
- The recommendations for an initial dose of 400 mg daily is based on analyses of two randomized phase III trials that have compared two doses (400 mg versus 800 mg/day) of imatinib. A higher dose has not been shown to increase overall survival. There is a discrepancy in two-year progression-free survival, with one trial reporting a significant advantage in progression-free survival with the higher dose and one trial finding no significant difference.
- The treatment duration in responding patients, particularly those who achieve a clinical complete response is as yet undefined. For practical purposes, until further studies are done:
  - Patients with stable disease should be treated until disease progression. Phase III data beyond two years of continued therapy are not available.
  - Treatment should be discontinued if serious toxicity develops. The dose may be reduced or interrupted to allow side effects to resolve, then may be re-started.
  - For patients who achieve a complete clinical response and radiologic remission with imatinib, treatment should be continued indefinitely until further data is available regarding the optimum duration of therapy in such patients. This is based on the observation that the majority of patients relapse following cessation of therapy with imatinib.
- At present, there is insufficient evidence to support the use of imatinib as an adjuvant therapy in patients who have undergone initial complete resection of disease.
- Surgery may be considered for patients whose disease is rendered resectable following imatinib therapy or to remove residual disease in selected patients.
- At present, the use of neoadjuvant imatinib is not recommended.

Key Evidence

- Evidence was available from two parallel phase III randomized trials (one in abstract form) that compared two doses of imatinib. None of the trials compared imatinib with a control.
- Across trials, response rates ranged from 41 to 65%, with an additional 32 to 36% of patients achieving stable disease.
- No quality-of-life data were reported from clinical trials of imatinib.
- Phase III trials comparing 400 mg and 800 mg of imatinib daily detected no survival advantage with the higher dose but a significant increase in side effects. Data on progression-free survival are mixed, with one trial reporting a significant improvement with the higher dose and a second trial finding no significant difference.

Key Evidence added in 2015:

- The diagnostic criteria for GIST have evolved in recent years. Specifically the discovery of the immunohistochemical marker for DOG 1 has led to its inclusion in the pathological work up of suspected GISTs. DOG-1 may also be expressed in GISTs that are c-kit negative (1-3)
- c-kit negative GISTs have been demonstrated to respond to Imatinib and therefore the it is reasonable to include patients with definitive GISTs which are DOG-1 positive but C-kit negative in adjuvant and metastatic treatment algorithms.
- The inclusion of this small population of patients is not anticipated to cause harm; in fact overall benefit is projected.

Future Research

Future research should include trials that:

- Examine quality of life for elderly patients with GIST treated with imatinib.
- Examine the use of imatinib as an adjuvant or neoadjuvant treatment for patients with GIST.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Evidence-based Series 11-7: Section 2

Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours: A Systematic Review

S. Verma, J. Younus, D. Stys-Norman, A.E. Haynes, M. Blackstein, and the Sarcoma Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care, Cancer Care Ontario

Please see the EBS 11-7 Guideline Review Summary and the Document Assessment and Review Tool for summary of updated evidence published between 2006 and 2011.

Report Date: April 6, 2006

QUESTION

Does treatment with imatinib mesylate (Gleevec™) have palliative benefit, in terms of tumour response, disease progression, survival or quality of life, for patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining)?

INTRODUCTION

GISTs are relatively rare tumours, representing 5% to 30% of all mesenchymal tumours of the gastrointestinal tract. (1,2). They are most common in the stomach (39% to 70%) and the small intestine (20% to 32%), whereas the colon, rectum and esophagus are sites of disease in less than 15% of cases (2,3). GISTs occur predominantly in individuals over 40 years of age, with the majority occurring between the ages of 55 to 65 (2,4).

The current standard of care for patients with resectable GIST is surgery which results in a five-year survival rate of 54% (2). It has become increasingly apparent that while

complete resection of GISTs is the mainstay of treatment, it is not always curative. In patients with apparent localized, completely resected disease, recurrences may be observed in up to 40% of patients. Furthermore, in patients with more locally advanced disease, complete resection of visible disease results in recurrences in up to 90% of cases.

Until recently, there has been no effective treatment for patients with unresectable or metastatic GIST. These tumours are resistant to conventional chemotherapy (3,5), and the close proximity and potential toxicity to surrounding tissues makes radiation therapy unsuitable (3,5). As a consequence, such patients have usually been offered palliative (symptom-oriented) care or entry into phase I/II trials with novel agents.

Over-expression of the KIT receptor (CD117) is an integral immunohistochemical feature of GISTs, and mutations in c-KIT have been observed in 85 to 100% of GISTs. (6-8). Rubin et al (6) have reported that constitutive phosphorylation of the KIT receptor without ligand activation was noted in all GISTs examined in their series and that c-KIT mutations were not confined to higher-grade tumours; mutations were also detected in histologically benign GISTs.

Imatinib mesylate is a targeted therapy aimed specifically at blocking the phosphorylation of tyrosine kinase receptors (9). Imatinib was initially developed to block the BCR-ABL fusion protein in chronic myeloid leukemia (CML) (10). However, in a study by Tuveson et al (11), imatinib was found to completely inhibit the phosphorylation of the KIT receptor, thus halting cell proliferation and eventually leading to cell apoptosis. As a result, imatinib has been studied in patients with metastatic or unresectable GISTs, and the drug has now been approved by the U.S Food and Drug Administration (FDA) for use in CML and GISTs. (12).

There are many ongoing and completed trials that have attempted to determine the appropriate patient population for imatinib, as well as the optimal dosage and duration of treatment. The Sarcoma Disease Site Group (Sarcoma DSG) of the Program in Evidence-based Care (PEBC) of Cancer Care Ontario (CCO) decided that a practice guideline based on an unbiased systematic review of the literature was required to address these points.

METHODS

This systematic review was developed by the CCO's PEBC, using the methods of the Practice Guidelines Development Cycle (13). Evidence was selected and reviewed by three members of the PEBC's Sarcoma DSG and methodologists. Members of the Sarcoma DSG disclosed information on potential conflict of interest. All members reported that they had no potential conflict of interest.

This systematic review is a convenient and up-to-date source of the best available evidence on imatinib mesylate for unresectable or metastatic GIST expressing KIT (CD117+) and primarily comprises mature randomized controlled trial (RCT) data. That evidence forms the basis of a clinical practice guideline developed by the Sarcoma SDG and published on http://www.cancercare.on.ca. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

Searches of MEDLINE (1996 through December 2005), EMBASE (1996 through December 2005), PREMEDLINE (to June 25, 2003), and the Cochrane Library (2005, Issue 4) were undertaken. Search terms used included "gleevec", "glivec", "imatinib", or "STI571" in combination with "GIST" or "gastrointestinal stromal".

In addition, the conference proceedings of the American Society of Clinical Oncology (ASCO) were searched for abstracts of relevant trials, for the years 1996-2005. The Canadian

Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were eligible for inclusion in the systematic review conducted for this practice guideline if they were:

- Abstracts or full reports of randomized phase II and III clinical trials of imatinib mesylate as treatment for adult patients (≥15 years of age) with unresectable or metastatic GIST. That reported data on one or more of the following outcomes: objective response rate, stable disease rate, progression-free survival, overall survival, toxicity, and quality of life.
- Systematic reviews (meta-analyses or practice guidelines).

Exclusion Criteria

Articles were excluded if they were retrospective studies, editorials or letters or articles that were published in languages other than English. A post hoc decision was made to remove all phase I studies that were originally included in the results section of this document as there were available data from phase II and phase III trials.

Synthesizing the Evidence

Data were not pooled as only abstract/interim data were available for two of three studies (14,15).

RESULTS

Literature Search Results - Study Characteristics

The literature search identified three relevant clinical trials of imatinib:

- The phase III Intergroup Study S0033 of two doses (400 versus [vs.] 800 mg/day) of imatinib in patients with unresectable or metastatic GIST, reported in four abstracts (15-18).
- The European Organization for Research and Treatment of Cancer (EORTC)-STBSG, Italian Sarcoma Group (ISG), and Australasian Gastro-Intestinal Trial Group (AGITG) phase III study, comparing two doses of imatinib in advanced GIST, was fully published in 2004 (19). An interim analysis of patients who crossed over to imatinib 800 mg was published in 2005 (20).
- A French Sarcoma Group phase III trial of continuous versus intermittent imatinib therapy reported in three abstracts (14,21,22)
- Two phase II randomized trials comparing doses were reported in a published paper (23) and abstract (24).

Two practice guidelines for the management of GISTs were identified (25,26). Due to the lack of mention of a systematic review of the literature and the substantial differences between those guidelines and ours, particularly in the continuation of care after the progression of the disease, those guidelines will not be mentioned in the results.

Phase III trials

Two large international randomized trials—the Intergroup Study S0033 (15) and the EORTC-STBSG/ISG/AGITG study (19)—used the same design to compare the effects of two different doses of imatinib on overall and disease-specific survival in adult patients with CD-

117-expressing metastatic or unresectable GIST. The studies were designed to detect a 10% difference in progression-free survival between dose levels. The results are reported in Tables 1 and 2 below; data from the Intergroup Study S0033 are available in abstract form only.

The trials were not double blind. In both studies, prior chemotherapy was allowed. Patients were stratified by performance status (PS) and measurable disease (yes or no) and then randomized to receive 400 mg of imatinib either once- or twice-daily (total daily dose 800 mg). Patients who demonstrated progression were considered for crossover to the higher dose. In the S0033 Intergroup Study, 746 patients were randomized and 88 of 164 patients (53.7%) in the 400 mg group crossed over to the 800 mg/day group because of progression. In the EORTC study, two groups of 473 patients were randomized to imatinib 400 mg once daily or twice daily (800 mg). The primary endpoint was progression free survival (PFS). Secondary endpoints included overall survival, response to treatment, and toxicity.

The French Sarcoma Group also conducted a multicentre phase III trial (BFR14) reported in abstract form(14,21,22). Patients were randomized after one year of imatinib therapy to continuous treatment or interruption of therapy. As of December 2003, 159 patients had begun the initial one-year treatment with imatinib. Of 74 patients who had completed one year of treatment, 46 have been randomized to receive continuous (23 patients) or interrupted (23 patients) treatment with imatinib. In that study, prognostic factors for survival and PFS were also examined.

Phase II

In 2002, Demetri et al (23) published the full report of a multicentre open-label randomized phase II trial. One hundred and forty-seven patients with CD-117-expressing metastatic or unresectable GIST were randomized to either 400 or 600 mg of imatinib once daily. Nine patients whose tumours progressed on 400 mg were crossed over to the higher dose. The study was designed to estimate the response rate in each dose group with a 95% confidence interval (±8.4%) but was not powered to detect a difference between treatment groups. Response was assessed using computed tomography (CT) or magnetic resonance imaging (MRI). Fifty-one percent of patients had received one to seven prior chemotherapy regimens without objective tumour response. The trial was supported in part by a grant from Novartis Oncology (Basel, Switzerland). Eleven of the report authors consulted for or received grants from Novartis, and five authors were employees of and held equity in Novartis.

Outcomes

Evidence from all clinical trials is summarized in Tables 1 and 2 and presented in the text below.

Response Rate

Phase III

In the French Sarcoma Group study, of the 159 patients that had completed or were on the initial one-year treatment period with imatinib, the response rate was 52%, with a stable disease rate of 36% (14).

An interim analysis of 133 patients from the EORTC trial (20) who crossed over to imatinib 800 mg/day demonstrated disease progression that achieved a partial response or stable disease if the dose of imatinib was increased to 800 mg/day. Median time on treatment after crossover was 112 days. An estimated 77% of subjects no longer received treatment one year after crossover; discontinuation was due to disease progression in 88.4% of patients. Three patients (2.3%) had a partial response, 36 patients (27.1%) had stable disease, and 79 patients (59.4%) showed progression. Among those 39 patients, the median duration of

stabilization from crossover was 153 days (range 37-574 days). For the entire data set, the median duration of progression-free survival was 81 days. A total of 53.3% progressed or died within three months, and 18.1% were alive and progression-free after one year.

Multivariate regression analysis of data from 615 patients in the EORTC phase III trial reported that a high baseline hemoglobin level was the only predictor of tumour response (27). Favourable PFS was associated with good performance status, high hemoglobin, gastric origin of disease, and the presence of liver metastases.

In the S0033 trial, 88 of 164 patients that demonstrated progression crossed over to the higher dose group. Median duration of follow-up was 307 days (range 1-852 days). After crossover, five of 68 evaluable patients (7.4%) had demonstrated a partial response and a further 20 patients (29.4%) stable disease(15). Median PFS and overall survival were four and 19 months, respectively.

Phase II

Demetri et al (23) assessed response using computed tomography (CT) or magnetic resonance imaging (MRI). In total, 79 patients (53.7%) had a partial response, and 41 patients (27.9%) had stable disease. Response could not be evaluated in 7 patients (4.8%). No patient had a complete response. Early resistance to imatinib was noted in 20 patients (13.6%). In a phase II trial reported in an abstract by Doi et al, (24) 41% of patients had a partial response, 30% with stable disease and one case of progression.

Survival

Phase III

A published report was available only for the EORTC study (19); abstract reports for the S0033 Study provided limited data. (15) (Table 1) In the EORTC trial, PFS was superior with imatinib 800 mg/day versus 400 mg/day, although response and overall survival were not significantly different. The S0033 study, reported there was no significant advantage with respect to PFS or other outcome measures with the higher dose (15).The reason for that discrepancy in PFS results between the two trials requires further examination.

The EORTC study (19) reported that median follow-up was 760 days (25.3 months); one-year data were available for 98% of subjects, and two-year data were available for 58% of subjects. PFS at two years was 44% with imatinib 400 mg/day and 50% with imatinib 800 mg/day (p=0.026). Overall survival was 85% and 86% with the imatinib 400 mg and 800 mg/day, respectively, at one year and 69% and 74% in the two groups at two years (not significant [NS]).

The S0033 study (15) estimated that two-year survival rates were 78% for imatinib 400 mg/day, and 73% for imatinib 800 mg/day (NS). The two-year PFS estimates were 50% and 53% for the two dose groups, respectively (NS).

Thus, it appears that approximately 41-65% of patients with metastatic GIST following surgery and/or chemoradiotherapy will respond to imatinib 400 mg/day (15,19). The estimated PFS rate at one year was 64% with imatinib 400 mg/day (28), and two-year survival rate was estimated to be 69 -78% (15,19).

Phase II

Demetri et al (23) was the only study to discuss survival. That figure was extrapolated from the survival curve published.

Table 1. Response and survival data from randomized phase II & III clinical trials of imatinib for advanced or metastatic GIST.

Trial (reference)	Daily Dose (mg)	No. of pts	Median follow-up (mths)	RR[a] (%)	SDR (%)	PFS 2-yr (%)		Overall Survival 2 yr (%)
Phase III trials								
EORTC-ISG-AGITG (19)	400 800	473 473	25.3	50[b] 65[b]	NR	44 50	p=0.026	69 74
Intergroup Study S0033 (15)	400 800	746	25.2	43 41	32 32	50[c] 53[c]	>0.05	78 73
French Sarcoma Group (14)	400	159	12	52	36	NR		NR
Phase II trials								
Doi et al 2004 (24)	400 600	28 46	NR	55	41	NR		NR
Demetri et al 2002 (23)	400 600	73 74	9.5	49 58	32 24	NR		87[d]

Notes: AGITG – Australasian Gastro-Intestinal Trials Group, EORTC – European Organization for Research and Treatment of Cancer, ISG – Italian Sarcoma Group, No. – number, NR – not reported, PFS – progression free survival, pts – patients, RR – response rate, SDR – stable disease rate, yr(s) – year(s).
a (# complete responses + # partial responses)/number enrolled.
b Estimated from response curve.
c Estimates of progression-free survival.
d dose groups combined, one-year survival extracted from published survival curve.

Toxicity
See Table 2 for results.

Phase III

Toxicity reports from the phase III trials were based on 325 S0033 patients and 976 EORTC patients (16,19). Data were only presented by dose group for the EORTC study (19).

In the S0033 trial, 23% of patients experienced grade 3 or 4 adverse events (16). The most common adverse events requiring a dose delay/reduction were rash, edema, and gastrointestinal bleeding (18).

The EORTC trial (19) reported that a total of 152 patients (32.3%) on imatinib 400 mg/day and 237 patients (50.2%) on imatinib 800 mg/day had at least one grade 3 or 4 adverse event. Imatinib was the most probable cause of death in five patients, as a result of hepatic toxic events and bleeding. Imatinib could not be ruled out as a cause of death in a further 13 patients (1.4%). The most frequent adverse effects were anemia (93%) and granulocytopenia (42%), edema (80%), fatigue (74%), nausea (55%), and skin rash (37%), most of which were described as mild to moderate.

Phase II

Only one study reported that patients had experienced grade 3/4 toxicity (23). Therapy was generally well tolerated, although mild-to-moderate edema, diarrhea, and fatigue were very common. Gastrointestinal or intra-abdominal hemorrhage occurred in approximately 5% of patients. There were no significant differences in toxicity or clinical response between the two doses.

Table 2. Toxicity data from randomized phase II & III clinical trials of imatinib for GIST - percentage of patients with grade 3 or 4 adverse events.

Author, Year (reference)	Daily Dose (mg)	Anemia	Nausea/ Vomiting	Bleeding	Abdominal Pain	Edema	Fatigue	Rash	PDRD
Phase III trials									
Intergroup S0033 trial (16)	400 800	NR	4	4[a]	4	2	2	2	3
EORTC trial (19)[b]	400 800	7 17	5[c] 6[c]	3 8	NR	3 9	6 11	2 5	0.5
Phase II trials									
Doi et al 2004 (24)	400 600	NR	0 0	0 0	0 0	0 0	0 0	0 10.9	NR
Demetri et al 2002 (23)	400 600	1.4 2.7	1.4 1.4	4.1[a] 1.4[a]	1.4 0	1.4 1.4	0 0	2.7 2.7	NR

Notes: NR – not reported, PDRD – possible drug-related death
a gastrointestinal bleeding
b Only events reported in the table with a toxic effect in more than 2.5% of patients reported a p value of <0.0001 not including PDRD
c Nausea only

Quality of Life

No quality of life data were reported from clinical trials of imatinib. However, Demetri et al observed an improvement from baseline in performance status on imatinib in their phase II trial (23). After four months of treatment, 64% of patients had an Eastern Cooperative Oncology Group (ECOG) score of 0, indicating normal function, and 5% had scores of 2-3, indicating substantially impaired function; at study entry, 42% and 19% had scores of 0 and 2-3, respectively.

DISCUSSION

The dual observations that a large proportion of GISTs harbour c-KIT (CD117) mutations and that imatinib mesylate was able to selectively inhibit phosphorylation of the KIT receptor, thereby halting cell proliferation and leading to cellular apoptosis, led to a number of phase II trials of that agent in patients with metastatic or unresectable GISTs. Repetitively, important responses were observed in a tumour subtype where, until this time, no active therapy had been discerned. In the single arm phase II trial led by Verwiej et al, 27 GIST patients received 400 mg of imatinib daily. Of those patients, 4% had a complete response, 67% had a partial response and 16% had stable disease (29). Similar results were observed in two additional small phase II trials (30,31). Those trials contributed to an historical alteration of the management of GISTs, and it is clear that no studies could or would be performed where imatinib would be compared with no-treatment controls. Consequently, in our extensive search of the literature, no trials comparing imatinib versus no treatment or another systemic agent were retrieved.

Two randomized phase II trials, (23,24) focused on dose, response rate, and progression-free survival. Moderate response rates were reported in patients who received a minimum of 400mg daily to a maximum of 600mg daily. However, in those trials, higher doses were not associated with increased clinical benefits. An observed two-year survival of 87% in the trial by Demetri et al led to FDA approval of imatinib at a dose of 400 mg per day in metastatic/unresectable GIST patients (23). Subsequent larger RCTs have attempted to determine the influence of dose on response rate, progression free, overall and disease-specific survivals.

Dose and Administration

The EORTC and S0033 trials were similar in design and study populations (15,16). Interestingly, the two trials generated differing results with regards to dose effect: the EORTC trial (15) demonstrated a higher response rate (RR) (65 versus [vs.] 50%) in the 800 mg dose arm, while in the Intergroup trial, similar RR (43 vs. 41%) and SD rates were observed. Significant improvement in two-year PFS favoured the 800 mg in both trials, while two-year overall survival (OS) was not statistically different between the two doses in either study and ranged from 69 to 78%.

Patients who respond to imatinib often do so rapidly. However, in patients with demonstrated disease progression on 400 mg/day, approximately one-third will achieve further therapeutic activity with a dose increase to 800 mg/day (15,20). A higher dose is generally tolerable, although there appears to be a significant increase in anemia and fatigue (20). The routine use of a higher dose (800 mg/day) does not appear to be justified at this time, although one trial (19) did demonstrate a significant improve in PFS with the higher dose. Given the modest benefits and higher toxicity demonstrated with higher doses, the current standard recommended dose of imatinib should be 400 mg daily.

Imatinib clearly represents a significant advance in the treatment of GISTs. Consistently high rates of response or disease stability have been observed in all included studies. As there are no RCTs comparing imatinib to no treatment, it is not possible to state with statistical certainty whether treatment with imatinib confers a definite survival advantage.

Duration of Therapy

Data on the optimal duration of therapy are sparse. The third phase III RCT identified in our search, conducted by the French Sarcoma Group, essentially attempted to address this issue (14,21,22). In that trial, patients were randomized, after one year of therapy with imatinib to continuation or interruption of therapy. Sixty-six percent of patients who stopped imatinib experienced progression compared to 15.4% who continued therapy. Tumour control (objective response or stable disease) was re-established in three quarters of patients following re-introduction of imatinib. There was no significant different in overall survival at one year for interrupted versus continuous therapy. Another noteworthy finding was that, in the interrupted-treatment group, the risk of recurrence was similar in patients with complete remission (no evaluable disease) versus those with detectable disease at randomization (14). While those data suggest that treatment interruption may lead to a rapid flare-up of tumour growth, the sample size is small compared to the other RCTs and more mature data are needed. A small imaging study available in abstract form has also described a flare phenomenon after cessation of imatinib (32).

An important consideration in clinical practise is whether imatinib should be continued following documentation of CR. It is clear that a complete response with imatinib is unusual (11% CR rates were observed in the EORTC trial). Given the potential for toxicity (edema and nausea) with protracted therapy and the expense of the drug, it would seem reasonable to discontinue therapy after CR has been observed. However, patients demonstrating CR have been shown to have a similar risk of recurrence to those with detectable disease at randomization (14). Therefore, in these rare circumstances, it would seem prudent to continue therapy indefinitely until further data assessing this particular scenario is available.

Future Research

The future course of treatment of unresectable or metastatic GIST raises questions such as, what of patients who respond sufficiently to imatinib to permit surgical resection or debulking of the disease? In that growing population, there are numerous unanswered

questions. It is unclear if complete resection or "debulking" matters except in cases of previously unresectable tumours that may be operable following imatinib (33). At this time, there are insufficient studies or data to permit commentary on this subject.

Identifying potential markers of imatinib treatment response is still in its preliminary stages. A subgroup analysis of patients from the S0033 trial reported KIT mutations in 280 of 324 eligible patients (86.4%) and PDGFRA mutations in an additional three patients (0.9%) (34). Objective response (OR) was more likely in tumours expressing an exon 11 KIT mutation (OR 67%) versus those with an exon 9 mutation (OR 40%) or no kinase mutation (OR 39%). Multivariate analysis confirmed that a KIT exon 11 genotype was the best predictor of OR. However, OS between patients with an exon 11 mutation versus another KIT mutation or wild-type GIST was not significantly different.

Blackstein et al (35) conducted a separate unplanned retrospective analysis of a larger group of subjects from the S0033 trial. A total of 377 of 414 patients (91.1%) demonstrated a KIT-positive GIST, 14 (3.4%) had KIT-negative GIST, and 16 (3.9%) did not have a GIST. Eight KIT-negative GISTs were genotyped. A mutation in KIT or PDGFRA was found in 4 and 3 tumours, respectively. OR and PFS were not significantly different in KIT-negative versus KIT-positive GISTs; the estimated two-year PFS was 43% and 49%, respectively. It is clear that the selection of patients using sophisticated molecular or 'mutational' analyses requires further inquiry prospectively.

Furthermore, the very mode of action of imatinib confines its use to GISTs that express the KIT oncogene. Numerous mutations of the oncogene have been described, the most common being the juxtamembrane domain (exon 11) (1,36,37). One small case series has proposed four mechanisms of imatinib resistance: target resistance due to mutation, by overexpression, target modulation, and functional resistance, characterized by KIT or PDGFRA activation but with the mutation occurring outside the juxtamembrane region (exon 11) (38). This hypothesis requires further validation but suggests an increasingly important role of mutational analysis as a guide to treatment.

However, the scope of this guideline does not permit comment on histopathological, immunohistochemical, or molecular parameters or techniques that confirm the diagnosis of GIST or identify subsets of patients most likely to respond to imatinib. Those topics will be the subject of a future Sarcoma DSG summary/technology assessment.

Conclusion

The optimal duration of imatinib therapy for patients with metastatic GIST has not been established. However, two phase III trials have demonstrated the benefit of imatinib 400 mg/day for up to two years. Imatinib 400 mg/day may be continued for up to two years of continued dosing, with dosing reduced or interrupted according to patient tolerability. In patients who achieve a CR, treatment should ideally be continued due to the high risk of recurrence after cessation of therapy. However, cost and toxicity should be considered in these circumstances.

During therapy, patients should be monitored for adverse effects such as nausea, vomiting, anemia, bleeding, and edema (particularly periorbital edema). Severe nausea and vomiting may necessitate discontinuation of therapy. For those patients who develop edema, it may be appropriate to stop therapy for a short time and then re-start imatinib if the edema improves. Gastrointestinal bleeding should be investigated immediately, and a surgical opinion should be sought. In patients who progress despite optimum therapy, treatment should be discontinued and enrolment in a clinical trial should be considered.

ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database (http://www.cancer.gov/search/clinical_trials/) and the Current Controlled Trials database (http://www.controlled-trials.com) on the Internet were searched for reports of new or ongoing trials. The databases were last searched December 8, 2005 and no ongoing phase III trials were found.

CONFLICT OF INTEREST

The members of the Sarcoma DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. No potential conflicts were declared.

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For a complete list of Sarcoma Disease Site Group members,
please visit the CCO Web site at http://www.cancercare.on.ca/.

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Evidence-based Series 11-7: Section 3

Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours: Guideline Development and External Review - Methods and Results

S Verma, J Younus, D Stys-Norman, A.E Haynes, M Blackstein, and the Sarcoma Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario.

Please see the EBS 11-7 Guideline Review Summary and the Document Assessment and Review Tool for summary of updated evidence published between 2006 and 2011.

Report Date: April 6, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO).(1) The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle.(1,2) The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series:
Each Evidence-based Series comprises three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results*. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review

This evidence-based series was developed by the Sarcoma DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on imatinib mesylate (Gleevec™) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The Sarcoma DSG focused their discussion on the evidence for imatinib as a treatment for adult patients with unresectable or metastatic GIST. Three of the trials (two phase III and one phase II) were only available in abstract form (3-8). Therefore, full data was not available for all outcomes, thus making pooling of the results inappropriate. The remaining phase II trial by Demetri et al (5) was available as a fully published report. The trial received funding from Novartis Oncology. Since those trials (3-8) constituted the best available evidence for the use of imatinib for GISTs, the Sarcoma DSG agreed that those trials should be included in this practice guideline report.

The Sarcoma DSG also discussed the fact that no trials compared imatinib to no treatment. Therefore, it is not possible to state with absolute statistical certainty that treatment with imatinib confers a definite survival advantage. However, the trials do show response rates ranging from 41% to 58%. If the stable disease rate is added to the response rate, the result is an increase to 73% to 82%. Also, progression-free and overall survival in those trials is markedly higher than in historically untreated patients. Therefore, the Sarcoma DSG agreed that it is reasonable to assume that the observed progression-free and overall survival rates are both relevant and meaningful.

Another point of discussion was the question of dose level. There has been no established benefit for doses higher than 400 mg daily. In addition, the higher toxicity associated with higher doses of imatinib would suggest that there is no clear benefit to starting patients at higher doses. Therefore, the Sarcoma DSG recommends that patients should start on a dose of 400 mg daily.

Finally, in terms of treatment duration, there are limited data to form definitive recommendations for situations such as stable disease, disease that is rendered resectable, or complete remission of disease. However, given the data that are available in the trials conducted to date, as well as the potential toxicity and the difficulty in discerning complete remission with reasonable certainty, the Sarcoma DSG agreed on the following:

1. For stable disease, treatment should be discontinued if the disease progresses or toxicity develops;

2. For disease that is rendered resectable, surgery should be considered;
3. For complete clinical response and radiologic remission, the discontinuation of therapy two months after CR has been observed would be reasonable.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series the Sarcoma DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review March 18, 2004)

Target Population

These recommendations apply to adult patients with unresectable or metastatic GISTs expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining).

Recommendation

- In patients with KIT expressing (CD117+), unresectable or metastatic GIST, treatment with imatinib is a recommended therapeutic option.
- Until additional data becomes available, imatinib should be prescribed at a dose of 400 mg daily. The optimal duration of therapy in responding patients or in those patients who achieve a complete clinical and/or radiological remission has not yet been defined.
- When possible, eligible patients with GISTs should be considered for entry into clinical trials.

Qualifying Statements

- The recommendation for a dose of 400mg daily is based on *interim* analyses of two randomized phase III trials that have compared two doses (400 mg vs. 800 mg) of imatinib. Until full analyses are available, data supporting a higher dose of imatinib are scant.
- The treatment duration in responding patients, particularly those who achieve a clinical complete response, is undefined. For *practical purposes*, until further studies are done, patients with stable disease should be treated until disease progression.
- For patients whose disease is rendered resectable, surgery should be considered.
- For patients who achieve a complete clinical response and radiologic remission with imatinib, treatment should be continued for at least two months beyond documentation of complete response.
- At present, there is no evidence that would support the use of imatinib as an adjuvant therapy in patients who have undergone initial complete resection of disease.

Methods

Practitioner feedback was obtained through a mailed survey of 179 practitioners in Ontario (two pathologists, 26 radiation oncologists, 45 medical oncologists, and 106 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on March 24, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Sarcoma DSG reviewed the results of the survey.

Results

Ninety-five responses were received out of the 179 surveys sent (53% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 41 indicated that the report was relevant to their clinical practice, and they completed the survey. One respondent who indicated that the report was not relevant to them completed the survey, but the data from this respondent was not included in the analysis below. Key results of the practitioner feedback survey are summarized in Table 3.

Table 3. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Introduction" section of the report, is clear.	40 (98)	1 (2)	0 (0)
There is a need for a clinical practice guideline on this topic.	38 (93)	3 (7)	0 (0)
The literature search is relevant and complete.[1]	37 (92)	3 (8)	0 (0)
The results of the trials described in the report are interpreted according to my understanding of the data.[1]	40 (100)	0 (0)	0 (0)
The draft recommendations in this report are clear.	40 (98)	1 (2)	0 (0)
I agree with the draft recommendations as stated.	40 (98)	1 (2)	0 (0)
This report should be approved as a practice guideline.[1]	35 (88)	4 (10)	1 (2)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	27 (66)	4 (10)	10 (24)

[1] One practitioner did not respond to these questions.

Summary of Written Comments

Eleven respondents (27%) provided written comments. The main points contained in the written comments were:

1. Three practitioners believed that this practice guideline would be helpful in treating patients with GIST, which are relatively rare tumours.
2. Two practitioners noted that GISTs are rare tumours and they were concerned that, by the time they see another patient with GIST, the guideline may be obsolete.
3. One practitioner noted that quality of life, especially for older patients with diarrhea, should be studied in future trials of imatinib for GISTs.
4. One practitioner had several concerns:
   i. What should be done for patients (with or without symptoms) with residual disease after surgery but no demonstrable disease on CT scan?
   ii. Should one or two dimensions be used to assess progression?
   iii. Should diuretics be advised for fluid retention?
5. Three practitioners expressed concern that the only available evidence is from phase II trials and abstracts of phase III trials, although two of these practitioners agreed with the conclusions of this guideline.
6. One practitioner stated that patients with recurrent or unresectable GIST should be closely followed in order to obtain unbiased survival data and that this should be done at arm's length from Novartis.
7. One practitioner cited studies presented at ASCO 2004 that should be included in the recommendations.

Modifications/Actions

1. The Sarcoma DSG acknowledges that, because GISTs are relatively rare, many practitioners have limited experience treating patients with this type of tumour. The aim of this practice guideline is to provide recommendations for the treatment of adult patients with unresectable or metastatic GIST.
2. Again, the Sarcoma DSG agrees that GISTs are rare and that, for many practitioners, many years might elapse between patients who present with GIST. The Sarcoma DSG will perform update searches of the literature on a yearly basis and incorporate any new literature into the practice guideline. The objective is to maintain this practice guideline as the most up-to-date source of information for the treatment of adult patients with unresectable or metastatic GIST.
3. The Sarcoma DSG acknowledges that quality of life for older patients with diarrhea is an important consideration. Therefore, the Sarcoma DSG has added a "Future Research" section within the practice guideline that addresses this specific concern.
4. The Sarcoma DSG offers the following comments/suggestions:
   i. This guideline does not address the use of imatinib as an adjuvant/neoadjuvant treatment, nor are any data available regarding the use of imatinib for residual disease after surgery. Therefore no recommendations are made by the Sarcoma DSG with regard to patients with residual disease after surgical resection.
   ii. Typically, practitioners should use Response Evaluation Criteria in Solid Tumours (RECIST) criteria to measure response or progression, but for practical purposes, uni- or bi-dimensional measurements may be used.
   iii. The Sarcoma DSG agrees that toxicities due to treatment with imatinib are a concern, and that toxicities are best managed by withdrawal of the drug.
5. The Sarcoma DSG acknowledges that the evidence for imatinib has limitations, but at this time it is the only available evidence. As there is no treatment for metastatic or unresectable GIST, the available response and toxicity data cannot be ignored. Therefore, the Sarcoma DSG feels that the available evidence is sufficient as a basis for the recommendations made in this practice guideline report.
6. The Sarcoma DSG acknowledgement that additional data are needed, especially with regard to survival for patients with unresectable or metastatic GIST, is stated in the Recommendations and Future Research sections of this practice guideline report. Ideally, clinical trials of imatinib should have limited, or no, involvement with pharmaceutical companies.
7. All but one of these abstracts has been incorporated in the present draft. The Demetri et al study was excluded since it was a phase I/II trial of SU11248 and did not meet the requirements for inclusion.

PRACTICE GUIDELINE

This practice guideline report reflects the integration of the draft recommendations with feedback obtained from the external review process. The report has been approved by the Sarcoma DSG and circulated to the members of the Report Approval Panel (RAP) for review and approval.

Report Approval Panel

The report was reviewed and approved in March 2006by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included:

1. The evidence did not answer the practice guideline questions and did not support the recommendations as presented by the DSG. There were no trials comparing imatinib against the standard treatment or best supportive care. The trials were dose-comparisons/continuous versus intermittent. As a result, the recommendations ought to be reconsidered and modified
2. The report was text-heavy in the Introduction and Discussion, which needed to be streamlined and revised to coincide with the topic and recommendations
3. The results were presented in a manner that was difficult to follow and required restructuring.

Modifications/Actions

1. It was acknowledged that there were no RCTs comparing imatinib to no treatment or best supportive care thereby making it difficult to statistically quantify the benefits for progression free survival and overall survival conferred by imatinib. The Sarcoma DSG has concluded that such trials will never be performed in the future in patients with unresectable or metastatic GISTs. In framing its recommendations, the DSG has also borne in mind the fact that treatment with imatinib in such patients has already gained wide acceptance among oncologists internationally.
2. The Introduction and Discussion were revised to enhance the topic of best course of treatment for unresectable and metastatic GIST patients and provide a clearer explanation in the Discussion why the recommendations were made, in light of the evidence.
3. The Results section was revised with subheadings and outcomes separated under those headings to improve the flow of text.

Policy Review

This practice guideline report was submitted to the Policy Advisory Committee (PAC) of CCO's New Drug Finding Program for the March 2004 meeting, in order to obtain funding for imatinib mesylate in the treatment of adult patients with unresectable or metastatic GIST expressing KIT (CD117+). Imatinib offers a high rate of response or disease stability for a disease for which there has previously been no treatment. Imatinib is currently available via the Ontario Drug Benefits (ODB) Section 8 process and will remain there as the process works well, PAC agreed with the recommendations of this practice guideline report and suggested that an additional qualifying statement be added stating that there is currently no evidence to support the use of imatinib as an adjuvant treatment in patients who have undergone initial complete resection of disease.

Funding

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1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
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3. Benjamin RS, Rankin C, Fletcher C, Blanke C, von Mehren M, Maki R, et al. Phase III dose-randomized study of imatinib mesylate (STI571) for GIST: Intergroup S0033 early results [abstract]. Proc Am Soc Clin Oncol. 2003;22:Abstract 3271.
4. Casali PG, Verweij J, Zalcberg J, Le Cesne A, Reichardt P, Ray-Coquard I, et al. Imatinib (Glivec) 400 vs 800 mg daily in patients with gastrointestinal stromal tumors (GIST): a randomized phase III trial from the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group (ISG), and the Australasian Gastro-Intestinal Trials Group (AGITG). A toxicity report. Proc Am Soc Clin Oncol. 2002;21:Abstract 1650.
5. Demetri, G. D., Rankin, C., Fletcher, C., Benjamin, R. S., Blanke, C., von Mehren, M., et al. Phase III dose-randomized study of imatinib mesylate (Gleevec, STI571) for GIST: intergroup S0033 early results. [abstract]. Proc Am Soc Clin Oncol 2002;21:Abstract 1651
6. Patel SR. Early results from randomized phase III trial of imatinib mesylate for gastrointestinal stromal tumors [abstract and commentary]. Curr Oncol Rep. 2003;5(4):273.
7. Ryu MH, Kim TY, Chang HM, Lee H., Kim JS, Kim WK, et al. Efficacy of imatinib mesylate in metastatic or unresectable malignant gastrointestinal stromal tumor (GIST). Proc Am Soc Clin Oncol. 2003;22:Abstract 3312.
8. Verweij J, Casali PG, Zalcberg J, Le Cesne P, Reichard P, Blay J-Y, et al. Early efficacy comparison of two doses of imatinib for the treatment of advanced gastro-intestinal stromal tumors (GIST): Interim results of a randomized phase III trial from the EORTC-STBSG, ISG and AGITG. Proc Am Soc Clin Oncol. 2003;22(Abstract 3272):81.

EBS 11-7 Document Assessment and Review Tool.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	11-7: Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours
Date of current version	6 April 2006
Clinical reviewer	Dr. Shailendra Verma
Research coordinator	Chika Agbassi
Date initiated	25 March 2011
Date and final results / outcomes	**25 April 2011- ENDORSED**[2]
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1. Yes, The data has continued to evolve with regards to dose and duration as well as the most appropriate tyrosine kinase inhibitor to be used in specific molecular mutations of GISTs.
	If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. Current recommendations are sufficient. 5 years have elapsed as of April 2011.
	If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. No
	If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • there is a designated research co-ordinator at the PEBC to carry out the literature search
	If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment & Review process evaluates the guideline **as is** and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this form and answer NO).	

Original Question(s):

Does treatment with imatinib mesylate (Gleevec™) have palliative benefit, in terms of tumour response, disease progression, survival or quality of life, for patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining)?

Target Population:

These recommendations apply to adult patients with unresectable or metastatic GIST expressing KIT (CD117+).

5b. **Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

Inclusion criteria:

Articles were eligible for inclusion in the systematic review conducted for this practice guideline if they were:

- Abstracts or full reports of randomized phase II and III clinical trials of imatinib mesylate as treatment for adult patients (≥15 years of age) with unresectable or metastatic GIST. That reported data on one or more of the following outcomes: objective response rate, stable disease rate, progression-free survival, overall survival, toxicity, and quality of life.
- Systematic reviews (meta-analyses or practice guidelines).

Exclusion criteria:

Articles were excluded if they were retrospective studies, editorials or letters or articles that were published in languages other than English. A post hoc decision was made to remove all phase I studies that were originally included in the results section of this document as there were available data from phase II and phase III trials.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):

Articles were eligible for inclusion in the systematic review conducted for this practice guideline if they were:

- Abstracts or full reports of randomized phase II and III clinical trials of imatinib mesylate as treatment for adult patients (≥15 years of age) with unresectable or metastatic GIST. That reported data on one or more of the following outcomes: objective response rate, stable disease rate, progression-free survival, overall survival, toxicity, and quality of life.
- Systematic reviews (meta-analyses or practice guidelines).

Exclusion criteria:

Articles were excluded if they were retrospective studies, editorials or letters or articles that were published in languages other than English. A post hoc decision was made to remove all phase I studies that were originally included in the results section of this document as there were available data from phase II and phase III trials

Search Period:

- 2006 to 2011 (Medline March wk 4 + Embase wk 14)

Brief Summary/Discussion of New Evidence:

Of 154 total hits from Medline + Embase, 6 references representing one meta-analysis and 4 RCTs were found. One RCT was already included in the existing guideline (rows highlighted in grey in the Table) and 3 RCTs are potentially new studies.

Interventions	Name of RCT	Phase of RCT	Population	Outcomes	Brief results	References
Imatinib (400mg) vs Imatinib (800mg	Meta-analysis of 2 RCTs			PFS OS	**PFS** was significantly better in the higher dose set HR=0.89 (95%CI; 0.79 to 1.00) P=0.04 **OS:** no significant difference was observed between arms.	Glabbeke V. et al. 2010
Imatinib cont. vs Imatinib inter.		III	advanced GIST patients CD117 expressed Age ≥18yrs ECOG PS 0-3 n=434	PFS*	**PSF** was significantly better in the continuous arm; 80% (95%CI: 33-38) against 16% (95%CI: 5-33) in the interrupted arm. P<0.0001 There was no difference in grade-3 AE between the two groups.	Cesne AL. et al 2010
		III	advanced GIST patients No previous IMA treatment CD117 expressed Age ≥18yrs ECOG PS 0-3 n= 182	PFS* OS, QoL	IMA interruption after one year usage resulted in rapid progression when compared to continuous IMA usage. P<0.0001. **OS** and **QoL** were not significantly different between arms.	Blay J et al 2007
Imatinib (400mg) vs Imatinib (600mg)	B2222	II	advanced GIST patients surgically incurable CD117 expressed ECOG PS <3 n=147	IMA(Cmin) OOBR,TTP	**TPP**: Those with C_{min}-Q <1,100ng/ml had lower TPP (11.3mos) compared to those with higher C_{min}-Q (>30mos). p= 0.002 **OOBR**: in those with KIT mutation, OOBR was 100% in those with higher C_{min}-Q against and 67% in those with C_{min}-Q <1,100ng/ml. P=0.001	Demetri GD et al 2009
				PFS, OS,TTR	There were no significant differences between arms in terms of TTR P<0.1039; TTP= p=0.3712 and OS	Blank CD et al 2008
	S0033	III	advanced GIST patients surgically incurable CD117 expressed Age≥15yrs ZPS 0-3 n= 746	OS,PFS	No significant difference between arms.	Blank CD et al 2008

ON GOING TRUALS
Retrieved from clinicaltrial.gov database

Interventions	Official title	Status	Protocol ID	Last Updated
Imatinib (400mg) vs Imatinib (600 or 800mg)	A Randomized, Phase 3 Study of Dose Escalation Versus No Dose Escalation of **Imatinib** In Metastatic GIST Patients With **Imatinib** Trough Levels Less Than 1100 Nanograms/mL		NCT01031628	March 16, 2011
Imatinib vs Nilotinib	A Randomized, Open Label, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Nilotinib Versus **Imatinib** in Adult Patients With Unresectable or Metastatic **Gastrointestinal Stromal Tumors** (GIST)	Recruiting	NCT00785785	October 11, 2010
Imatinib (400 or 600mg) vs masitinib (7.5 mg/kg/day)	A Prospective, Multicenter, Randomized, Open-label, Active-controlled, 2-parallel Group, Phase III Study to Compare Efficacy and Safety of **Masitinib** at 7.5 mg/kg/Day to **Imatinib** at 400 or 600 mg in Treatment of Patients With Gastro-intestinal Stromal Tumour in First Line Medical Treatment	Recruiting	NCT00812240	August 6, 2010
Imatinib low dose vs Imatinib high dose	Phase III Randomized, Intergroup, International Trial Assessing the Clinical Activity of **STI-571** at Two Dose Levels in Patients With Unresectable or Metastatic **Gastrointestinal Stromal Tumors** (GIST) Expressing the KIT Receptor Tyrosine Kinase (CD117)	Active, not recruiting	NCT00685828	July 24, 2009
Imatinib cont. vs Imatinib inter. (after 5yrs of treatment)	A Prospective Multicentric Randomized Study of **Glivec**® in Patients With Advanced **Gastrointestinal Stromal Tumors** Expressing c-Kit Comparing Treatment Interruption After 5 Years vs Treatment Maintenance	Recruiting	NCT00367861	November 1, 2007

AE = adverse event; **Cmin** = Trough concentration; **Cont** = continuous; **ECOG**= Eastern cooperative oncology group; **HR** = hazard ratio; **IMA** = imatinib**; INTER** = interrupted; **Mos**= months; **n**= number enrolled; **OOBR** = overall objective benefit rate; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression free survival; **QoL**= Quality of life;; **RT** = radiotherapy; **TTF** = time to treatment failure; **ZPS** = zubrod performance status

***** Primary outcome.

New References Identified (alphabetic order):

1. **Blanke CD**, Demetri GD, Von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. Journal of Clinical Oncology. 2008 01 Feb;26 (4):620-5.
2. **Blanke CD**, Rankin C, Demetri GD, Ryan CW, Von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. Journal of Clinical Oncology. 2008 01 Feb;26 (4):626-32.
3. **Blay JY**, Le Cesne A, Ray-Coquard I, Bui B, Duffaud F, Delbaldo C, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: The French sarcoma group. Journal of Clinical Oncology. 2007 20 Mar;25 (9):1107-13.
4. **Demetri GD**, Wang Y, Wehrle E, Racine A, Nikolova Z, Blanke CD, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. Journal of Clinical Oncology. 2009 01 Jul;27 (19):3141-7.
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6. **Van Glabbeke M**. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: A meta-analysis of 1,640 patients. Journal of Clinical Oncology. 2010 01 Mar;28 (7):1247-53.

Literature Search Strategy:

Medline

1. meta-Analysis as topic.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.

32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. (gastrointestinal? or GIT).tw.
39. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.
40. 38 and 39
41. exp gastrointestinal neoplasm$/
42. 40 or 41
43. (stromal adj tum?r).tw.
44. 42 and 43
45. gastrointestinal stromal tumo?r$/ or GIST/
46. 44 or 45
47. (metastat$ or advanced).tw.
48. 46 and 47
49. (Imitamib or Gleevec or Glivec).tw.
50. 48 and 49
51. (2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
52. 50 and 51
53. 37 and 52

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. (gastrointestinal? or GIT).tw.
34. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.

35. 33 and 34
36. exp gastrointestinal neoplasm$/
37. 35 or 36
38. (stromal adj tum?r).tw.
39. 37 and 38
40. exp gastrointestinal stromal tumor/ or GIST/
41. 39 or 40
42. (metastat$ or advanced).tw.
43. 41 and 42
44. (Imatinib or Gleevec or Glivec).tw.
45. 43 and 44
46. (2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ew.
47. 45 and 46
48. 32 and 47

Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6.Unlikely (NO) If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7.YES If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8.NO If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9.NO If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. Not Applicable. An **UPDATE**[4] will be posted on the website, indicating an update is in progress.

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

DSG Approval Date:	**May 31, 2011**
Comments from DSG members:	Literature review is complete and supports existing indications.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our Web site, **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the Document & Assessment Review form and on the document.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.