

BCCA Protocol Summary for Treatment of Advanced C-Kit Positive and C-Kit Negative Gastrointestinal Stromal Cell Tumours (GISTs) Using Imatinib (GLEEVEC®)

Protocol Code: SAAVGI
Tumour Group: Sarcoma
Contact Physician: Dr. Meg Knowling

ELIGIBILITY:

- Unequivocal Diagnosis of Gastrointestinal Stromal Tumour: Demonstration of c-kit protein using DAKO immunohistochemistry.
- Diagnosis of C-Kit Negative Gastrointestinal Stromal Tumour: Must be reviewed at central lab and diagnosis confirmed. Mutation analysis – if possible*.
- Advanced disease status – not amenable to surgery or other local therapy.
- No contraindication to use of imatinib, but it may not be indicated for patients with significant co-morbid illnesses which preclude quality of life, etc. (i.e. not appropriate for elderly patients with other life-limiting diseases or significantly impaired cognitive states).
- A “Class II Drug Registration Form” must be submitted at the time of initiation of treatment. Note separate boxes for c-kit positive and negative patients. For other indications, an “Individual use of Benefit Drug List Medication for an Undesignated Indication” form must be approved.

* Fresh/frozen tissue is preferable to paraffin block for mutation analyses though either specimen is acceptable. Please use GIST mutation analysis form previously circulated and FAX forms to originating lab as well as to Dr. Doug Horsman’s Lab at BC Cancer Agency – Vancouver Clinic
H:\EVERYONE\Sarcoma\Forms\Gist Mutation analysis request

EXCLUSIONS:

- Concurrent warfarin therapy

TESTS:

- Baseline and ongoing care:

	Months	1	2	3	4	5	6 +						
TESTS	Baseline	Weeks										Every 3 Months	Off Drug ^a
		2	4	6	8	10	12	14	16	18	20		
HPE ^b	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Toxicity		X	X	X	X	X	X	X	X	X	X	X	X
Assess Disease ^c	X			X							X	X	X
CBC ^d	X	X	X	X	X	X	X	X	X	X	X	X	X
LFT's ^e	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X												
Tumour c-kit	X												

^a Follow-up every month for the first year, then every 6 months for 2 years, then yearly.

^b Full history and physical examination

^c Including tumour size by physical and/or imaging

^d CBC and differential, platelet

^e Alkaline phosphatase, [AST](#), LDH, bilirubin

PREMEDICATIONS:

- Antiemetic protocol for low moderate emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BCCA Administration Guideline
Imatinib (GLEEVEC [®])	400 mg daily	PO

- Evaluate for response with clinical measures or evaluation of disease at 2 months then every 3 months.
- Continue drug until evidence of disease progression at which time the patient may be started on a higher dose of drug (see SAAVGIDD)

- In cases of localized progression, surgery or radiofrequency ablation might be appropriate and the patient maintained on lower dose of imatinib – discuss with contact physician.

DOSE MODIFICATIONS:

- Monitor for side effects using physical and laboratory evaluations monthly for 5 months, then every 3 months.

1. Hematological:

Toxicity	ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
Grade 1	greater than or equal to 1.5 - less than 2	or	less than LLN - 75	400 mg daily
Grade 2	greater than or equal to 1 - less than 1.5	or	greater than or equal to 50 - less than 75	400 mg daily
Grade 3	greater than or equal to 0.5 - less than 1	or	greater than or equal to 10 - less than 50	Hold until toxicity less than Grade 1, then resume at 300 mg daily. For second occurrence, hold until toxicity less than Grade 1, then resume at 200 mg daily.
Grade 4	less than 0.5	or	less than 10	Hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily. For second occurrence, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily.

- No dose reductions for Grade 3 or 4 anemia. Patients can be transfused or treated with erythropoietin (EPREX[®]).

2. Non-Hematological:

Toxicity	Dose
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Toxicity	Dose
Grade 2	<ul style="list-style-type: none"> ▪ Hold until toxicity less than or equal to Grade 1, then resume at the same daily dose ▪ If Grade 2 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily ▪ If Grade 2 toxicity recurs again, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily
Grade 3 or 4	<ul style="list-style-type: none"> ▪ Hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily ▪ If Grade 3 or 4 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily

- **Hemorrhage** – Intra-tumoral hemorrhage or tumor related intra-abdominal bleeding has been reported in an estimated 5% of cases and may be life threatening. This may not be manifested as obvious gastrointestinal bleeding as blood may be confined to the tumor, within the hepatic capsule, peritoneum or otherwise sequestered. Signs and symptoms of such an event may include hypotension, signs of hypovolemia, fall in hematocrit, localized pain, apparent rapid increase in size of mass, and CT results suggestive of bleeding. CT results should be evaluated carefully in light of this so that this syndrome is not mistaken for progressive disease.
- **Vomiting** – In the case of emesis related loss of imatinib, the dose should **NOT** be replaced.

PRECAUTIONS:

1. **Edema** – Facial and generalized body swelling commonly occurs and may be dose related. Track weight gain and use diuretics if excessive (greater than 2 kg in one week).
2. **Rash** is frequent and is not a reason to discontinue drug. Rarely toxic epidermolysis syndrome can occur.
3. **Congestive heart failure (CHF) with decreased left ventricular ejection fraction (LVEF)** has been reported in a very small proportion of patients treated with Imatinib. Careful clinical evaluation of patients who might be predisposed by reason of age or co-morbidities is recommended. If clinically CHF occurs: measure LVEF, start treatment of CHF and follow carefully. If further deterioration then discontinue Imatinib.
4. **Hepatotoxicity** with severe elevations of transaminases or bilirubin may be life threatening. Risk may be increased when imatinib is combined with other potentially hepatotoxic drugs. Management is dose reduction, interruption (median duration one week) or discontinuation (less than 0.5%) of imatinib.

5. **Drug interactions** may occur as imatinib is a potent competitive inhibitor of Cytochrome P450 enzymes (see BCCA Cancer Drug Manual).

Call Dr. Meg Knowing or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date Activated: 01 July 2002

Date Revised: 01 Nov 2011 (SGOT replaced by AST)

References:

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