BC Cancer Protocol Summary for Adjuvant Treatment of C-Kit Positive High Risk Gastrointestinal Stromal Cell Tumours Using iMAtinib

Protocol Code: SAAJGI
Tumour Group: Sarcoma
Contact Physician: Dr. Christine Simmons

ELIGIBILITY:
- Unequivocal diagnosis of Gastrointestinal Stromal Tumour (GIST): Demonstration of c-kit protein using DOG1 confirmation of diagnosis
- Diagnosis of c-kit negative GIST: Mutation analysis (if possible) should show one of the mutations known to respond to iMAtinib.
- Patient with completely resected GIST and high risk for recurrence:
  - 5-year relapse-free survival less than 60% as calculated using Gold Nomogram (Lancet Oncology 2009) (80 points or more)

EXCLUSIONS:
- Pregnancy

SPECIAL CAUTION:
- Concurrent warfarin therapy

TESTS:
- Baseline: (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Every 4 weeks for cycles 1, 2 and 3, then at least every 3 months: CBC and diff, platelets, creatinine, bilirubin, alkaline phosphatase, ALT, LDH
- Patients on warfarin should have more frequent INR monitoring at treatment initiation by physician who is managing anticoagulation
- Follow up: Clinical evaluation associated with imaging as below
  - Chest X-ray yearly
  - CT scan abdomen and pelvis
    - Years 1 – 3 (on drug): every 4 – 6 months
    - Years 4 – 5 (or 2 years off drug): every 3 – 4 months
    - Thereafter till 10 years: every 6 to 12 months at physicians discretion.
PREMEDICATIONS:

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

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamivudine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib</td>
<td>400 mg daily</td>
<td>PO</td>
</tr>
</tbody>
</table>

For 3 years after resection.

DOSE MODIFICATIONS:

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

1. Hematological:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>greater than or equal to 1.5 to less than 2.0</td>
<td>or less than LLN to 75</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Grade 2</td>
<td>greater than or equal to 1.0 to less than 1.5</td>
<td>or greater than or equal to 50 to less than 75</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Grade 3</td>
<td>greater than or equal to 0.5 to less than 1.0</td>
<td>or greater than or equal to 10 to less than 50</td>
<td>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.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>less than 0.5</td>
<td>or less than 10</td>
<td>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.</td>
</tr>
</tbody>
</table>
- No dose reductions for Grade 3 or 4 anemia. Patients can be transfused or treated with erythropoietin (EPREX®).

Non-Hematological:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 2</strong></td>
<td>- Hold until toxicity less than or equal to Grade 1, then resume at the <em>same</em> daily dose</td>
</tr>
<tr>
<td></td>
<td>- If Grade 2 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily</td>
</tr>
<tr>
<td></td>
<td>- If Grade 2 toxicity recurs <em>again</em>, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily</td>
</tr>
<tr>
<td><strong>Grade 3 or 4</strong></td>
<td>- Hold until toxicity less than or equal to Grade 1, then resume at 300 mg daily</td>
</tr>
<tr>
<td></td>
<td>- If Grade 3 or 4 toxicity recurs, hold until toxicity less than or equal to Grade 1, then resume at 200 mg daily</td>
</tr>
</tbody>
</table>

- **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 BC Cancer Drug Manual). Warfarin’s effect may be increased; monitor INR more closely especially at treatment initiation and at dose modifications of iMAtinib.
6. **Pregnancy:** Women of childbearing potential must be advised to use highly effective contraception during treatment.
7. **HBV infection reactivation risk:** Risk of Hepatitis B Reactivation can occur in

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*Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/legal.htm*
chronic HBV carriers after they receive BCR-ABL TKIs. All patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

8. **Progressive renal dysfunction:** loss of function may be greatest in first year and may contribute to development or worsening of some kidney diseases

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

References:


