Practical Management of Chronic Myeloid Leukaemia (CML) With Imatinib

March 2007
Introduction

Objective: To review key aspects of imatinib-therapy management in the practice setting

Topics covered

- Compliance and persistency
- Imatinib and myelosuppression
- Management of common haematological adverse effects (AEs)
- Management of common nonhaematological AEs
- Liver function testing
- Management of minimal residual disease (MRD)
Overview of Imatinib Safety, Tolerability, and Efficacy in CML

- Imatinib is generally well tolerated\(^1\)
- In the IRIS trial, \(<2\%\) of newly diagnosed patients withdrew from imatinib due to AEs\(^1\)
- Most AEs are mild to moderate and usually self-limiting\(^1-4\)
- Supportive measures can be taken to manage AEs
- Prompt, aggressive management of AEs is fundamental to optimal imatinib therapy\(^2,3\)
- Lack of management of AEs can lead to inadequate compliance and persistency\(^2,3\)
- Lack of treatment compliance and persistency can lead to suboptimal response\(^2,3\)

IRIS, International Randomised Interferon versus STI571 Study.

# Compliance and Persistency: Administration of Oral Agents

<table>
<thead>
<tr>
<th>Old cancer-treatment paradigm(^1,^2):</th>
<th>Parenteral drugs in supervised setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>New paradigm:</td>
<td>Oral drugs taken at home</td>
</tr>
<tr>
<td>New paradigm requires strong focus on compliance and persistency(^1-^5)</td>
<td>Persistency decreases over time</td>
</tr>
<tr>
<td></td>
<td>Increases risk for suboptimal response</td>
</tr>
<tr>
<td>Compliance and persistency are critical clinical issues in CML(^4,^5)</td>
<td>Risk for lack or loss of response (ie, resistance)</td>
</tr>
</tbody>
</table>

Factors Underlying Poor Adherence

Patient Related
- Cognitive impairment
- Psychopathology/mental illness
- Understanding need to take drug

Treatment Related
- AEs
- Inadequate supervision
- Route of administration

Environment Related
- Social attitudes towards treatment
- Family attitudes towards treatment
- Patient attitudes towards treatment
- Financial support

Physician Related
- Doctor-patient relationship
- Provision of information
- Communication
Compliance and Persistency

- Oral therapies are relatively new in oncology; only recently have health care providers recognized that adherence to oral therapeutic regimens may be an issue
  - Suboptimal adherence has been identified as a significant barrier to the effective use of oral cancer therapies\(^1,2\)
  - One of the first large studies\(^3\) (\(N = 4043\)) of adherence to imatinib regimens among cancer patients found that on average, over the 24-month study period:
    - Patients took only 75% of their prescribed medication
    - On average, patients consumed about 20% less than the prescribed dose of medication
    - Adherence began to decline after only 4 months
  - Testing medication blood levels may be a valuable tool to help identify suboptimal response due to nonadherence\(^4-6\)

Factors Potentially Affecting Compliance and Persistency With Imatinib Therapy

- Frequent treatment interruptions due to AEs
  - May promote idea that inconsistent dosing is normal part of therapy
- Lack of understanding on patient’s part that therapy must continue even though test results are normal
  - Nonadherence tends to begin when patients learn of first good response
- Economics of long-term therapy
Strategies for Improving Adherence to Imatinib Therapy

- Establish multidisciplinary team to manage outpatient oral therapy
- Monitor therapy closely and consistently
- Provide prompt and aggressive AE management
- Optimise communication and patient education
  - Inquire about adherence during each patient visit
    - Sample query to patient: How many days of tablets have you missed?
  - Advocate development of an at-home dosing routine
  - Share results of molecular monitoring to encourage more active participation in therapy ("know your numbers")
Management of Haematological Adverse Events
Imatinib and Myelosuppression

- Cytopaenias* consistently found in all studies
- Haematopoiesis in CML mainly derived from Ph+ stem cells
- Degree of myelosuppression expected because imatinib targets BCR-ABL
- Severe cases more frequent in accelerated-phase and blast-crisis disease
- No evidence that imatinib severely affects normal haematopoiesis
  - Toxicity to normal haematopoiesis restricted to high doses
  - Normal blood cell counts recovered in advanced-phase patients during continuous treatment

**Recommendation**
Monitor complete blood counts regularly with imatinib therapy

---

*Neutropenia, thrombocytopenia.
Ph+, Philadelphia chromosome positive.

## IRIS Study in CML: Grade 3/4 Haematological AEs

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (n = 553) (%)</th>
<th>IFN + Ara-C (n = 553) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>12.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*P < 0.001 difference in grade 3 plus grade 4 abnormalities between 2 treatment groups.*

Management of Haematological AEs: Chronic-Phase CML

| Neutropenia* and thrombocytopenia† | Interrupt therapy until ANC ≥1.5 × 10⁹/L and platelets ≥75 × 10⁹/L  
Resume therapy at previous dose  
  - Starting dose of 400 or 600 mg‡ daily |
| Recurrence | Interrupt therapy until resolution  
Resume therapy  
  - 300 mg‡ if starting dose was 400 mg  
  - 400 mg if starting dose was 600 mg |
| Anaemia | Treat with erythropoietin²,³ |
| Myelosuppression | Treat with growth factors⁴ |

*Neutropenia: ANC <1 × 10⁹/L. †Thrombocytopenia: platelets <50 × 10⁹/L. ‡Paediatric dosing equivalents: 400 mg adult dose = 260 mg/m²; 300 mg adult dose = 200 mg/m². §Granulocyte colony-stimulating factor.

ANC, absolute neutrophil count.

Managing Myelosuppression in Patients With Chronic-Phase CML

Starting dose 400 mg

ANC <1000 and/or platelets <50,000

Withhold imatinib

ANC ≥1500 and platelets ≥75,000

Resume imatinib at 400 mg

ANC <1000 and/or platelets <50,000

Withhold imatinib

ANC ≥1500 and platelets ≥75,000

Continue imatinib at 400 mg

ANC ≥1500 and platelets ≥75,000

Reduce imatinib to 300 mg

# Management of Haematological AEs: Advanced Phases of CML

Management of cytopaenias more difficult because of risk of jeopardising response \(^1\)

| Neutropaenia* and thrombocytopenia\(^\dagger\) | Interrupt therapy until ANC \(\geq 1.5 \times 10^9/L\) and platelets \(\geq 75 \times 10^9/L\)  
| | Resume therapy at previous dose  
| | - Starting dose of 400 or 600 mg\(^\dagger\) daily |
| Persistance | For 2 weeks  
| | Reduce dose to 300 mg\(^\dagger\)  
| For 4 weeks (unrelated to leukaemia) | Interrupt imatinib until ANC \(\geq 1 \times 10^9/L\) and platelets \(\geq 20 \times 10^9/L\),  
| | Resume treatment at 300 mg\(^\dagger\) |
| Anaemia | Possibly treat with erythropoietin\(^2,3\) |

*Neutropaenia: ANC <0.5 \(\times 10^9/L\). \(^\dagger\)Thrombocytopenia: platelets <10 \(\times 10^9/L\). \(^\dagger\)Paediatric dose equivalents: 600 mg adult dose = 340 mg/m\(^2\); 400 mg adult dose = 260 mg/m\(^2\); 300 mg adult dose = 200 mg/m\(^2\).

Managing Myelosuppression in Patients With Advanced Phases of CML

Starting dose 600 mg

ANC <500 and/or platelets <10,000*

Examine BM (marrow aspirate or biopsy); is cytopaenia related to leukaemia?

No†

Reduce imatinib to 400 mg

Cytopaenia persists >2 weeks

Reduce imatinib to 300 mg

Yes‡

Continue imatinib at 600 mg

Cytopaenia persists >4 weeks and still unrelated to leukaemia

Withhold imatinib

ANC ≥1000 and platelets ≥20,000

Reduce imatinib to 300 mg

BM, bone marrow.

*Occurring after at least 1 month of treatment. †Hypocellular marrow, no significant blast infiltrate, as decided by physician. ‡Hypercellular marrow, significant blast infiltrate, as decided by physician.

Management of Nonhaematological Adverse Events With Imatinib Therapy for CML
Oedema and Fluid Retention$^{1,2}$

- Superficial oedema is a dose-related AE occurring in >50% of patients
  - Mild to moderate
- Risk factors
  - Female sex, age >65 years, history of renal or cardiac insufficiency, or higher dose of imatinib
- Periorbital oedema most common
- Generalised fluid retention in <1% of early chronic phase
  - 2%-6% in other phases of CML

# Management of Oedema and Fluid Retention

<table>
<thead>
<tr>
<th>Old, high-risk patients</th>
<th>Management options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor for peripheral edema</td>
<td>Limit salt intake</td>
</tr>
<tr>
<td>If oedema detected</td>
<td>Topical phenylephrine 0.25% or hydrocortisone 1%</td>
</tr>
<tr>
<td>- Initiate diuretic therapy or increase diuretic dose</td>
<td>- Diuretics indicated in severe cases</td>
</tr>
</tbody>
</table>

- **Severe oedema**
  - Discontinue imatinib and control oedema with diuretic therapy
  - Restart imatinib—possibly at reduced dose—while maintaining or increasing diuretic

---

## Management of Nausea and Vomiting\(^1,2\)

<table>
<thead>
<tr>
<th>Nausea and vomiting can be avoided</th>
<th>Take with largest meal of day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea is often dose related</td>
<td>Split doses in half and take with separate meals</td>
</tr>
<tr>
<td>If nausea persists</td>
<td>Use antinausea medications*</td>
</tr>
</tbody>
</table>

*Eg, prochlorperazine, ondansetron.

**Management of Diarrhoea\(^1,2\)**

<table>
<thead>
<tr>
<th>Possible causes:</th>
<th>Managed by antidiarrheal medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT inhibition(^*)</td>
<td></td>
</tr>
<tr>
<td>Local irritation</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Highly expressed by cells that control intestinal motility.

Management of Muscle Cramps$^{1,2}$

Occur mainly in hands, feet, calves, and thighs
- Pattern, frequency, severity constant over time
- Resemble tetanic contractions

For symptomatic relief
- Quinine
- Ca$^{++}$ and Mg$^{++}$ supplements
- Nonsteroidal anti-inflammatory agents (NSAIDs)

Bone Pain and Arthralgias\textsuperscript{1,2}

- Bone pain reported in 20\%-40\% of patients taking imatinib
  - Aetiology may correlate with clearance of leukaemic cells from marrow
  - Onset usually in first month of therapy; frequently self-limited
  - Symptoms typically affect femur, tibia, hip, and knee joint

## Management of Bone Pain and Arthralgias

<table>
<thead>
<tr>
<th>No history of GI bleeding and platelet counts &gt;100,000/mm³</th>
<th>NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GI bleeding</td>
<td>NSAIDs + proton pump inhibitor</td>
</tr>
<tr>
<td></td>
<td>NSAIDs + H₂ histamine receptor blocker</td>
</tr>
<tr>
<td></td>
<td>COX-2 inhibitor</td>
</tr>
<tr>
<td>Platelet counts &lt; 100,000/mm³ or NSAIDs contraindicated</td>
<td>Acetaminophen (use with caution*)</td>
</tr>
<tr>
<td></td>
<td>Mild narcotic analgesics</td>
</tr>
</tbody>
</table>

*Controversy surrounds the safety of acetaminophen in patients receiving imatinib. One patient with accelerated-phase CML receiving imatinib died of hepatic failure after taking acetaminophen to treat fever. It was unclear whether the combination of drugs caused the death.

GI, gastrointestinal.
Management of Mild Skin Rash\textsuperscript{1,2}

Experienced by 30\%-40\% of patients but mild and self-limited

- Usually on forearms or trunk; occasionally on face
- Frequently pruritic
- Most commonly presents as erythematous, maculopapular lesions

Easily manageable with antihistamines or topical steroids

More severe cases managed with oral steroids

## Management of Severe Skin Rash

**Rare incidence of grade 3/4 exfoliative rashes (2%)**
- Imatinib interruption mandated
- Can be treated with oral corticosteroids
- Reintroduction of imatinib may be tolerated after resolution
- Imatinib should be reintroduced at a lower dose

---

**Permanent discontinuation in <1% of patients**

---

# Management of Fatigue

<table>
<thead>
<tr>
<th>Attributed in part to mild anaemia*</th>
<th>Often occurs early in treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resolves in many cases when haemoglobin returns to normal baseline levels</td>
</tr>
</tbody>
</table>

**Mild to moderate fatigue may persist after normalisation of haemoglobin level**

*Haemoglobin decreases by <2 g/dL.*

Incidence of Hepatotoxicity

- Severe elevations of liver enzymes in patients with CML
  - Transaminases or bilirubin, <3%
- Manage with dose reduction or interruption
- Median duration of episodes of liver toxicity was ~1 week
- <0.5% of patients required permanent discontinuation of imatinib because of hepatic AEs
- Liver function tests should be monitored regularly before initiation of therapy and monthly, or as clinically indicated

Renal Insufficiency

- No clinical studies were conducted with imatinib in patients with decreased renal function
  - Studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range
- Imatinib and its metabolites are not significantly excreted via the kidney
- Since the renal clearance of imatinib is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency
- In severe renal insufficiency, caution is recommended

Data on file. Basel, Switzerland: Novartis Pharma AG.
# Management of Liver Transaminase Elevations

<table>
<thead>
<tr>
<th>Usually managed with dose reduction or treatment interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interrupt imatinib therapy if</strong></td>
</tr>
<tr>
<td>- Bilirubin levels $&gt;3 \times$ IULN</td>
</tr>
<tr>
<td>- Liver transaminase levels $&gt;5 \times$ IULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resume therapy when</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bilirubin levels $&lt;1.5 \times$ IULN</td>
</tr>
<tr>
<td>- Liver transaminases $&lt;2.5 \times$ IULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imatinib may be resumed at a reduced daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult doses</strong></td>
</tr>
<tr>
<td>- From 400 mg to 300 mg or from 600 mg to 400 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paediatric doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- From 260 mg/m$^2$/d to 200 mg/m$^2$/d or from 340 mg/m$^2$/d to 260 mg/m$^2$/d</td>
</tr>
</tbody>
</table>

IULN, institutional upper limit of normal.

Data on file. Basel, Switzerland: Novartis Pharma AG.
Imatinib: Carcinogenicity

• Incidence rate of cancers observed in patients treated with imatinib does not differ from that of the general population

• Compared with the general population, patients treated with imatinib have
  – No increased overall incidence of second malignancies
  – No increased incidence of bladder, kidney, or prostate tumors

Imatinib and Pregnancy

- Women of childbearing years should be advised to avoid becoming pregnant during imatinib therapy
- Limited data on use of imatinib in pregnant women
  - Animal studies have shown reproductive toxicity
  - If a patient becomes pregnant during imatinib therapy, then she should be apprised of the potential hazard to the foetus
- Women should be advised against breastfeeding during therapy with imatinib

Substances That May Affect Imatinib Plasma Concentrations

Drugs that may INCREASE imatinib plasma concentration

- Clarithromycin
- Erythromycin
- Ketoconazole
  (IM: $C_{max} \uparrow$ by 26%; $AUC \uparrow$ by 40%)*
- Itraconazole

Drugs that may DECREASE imatinib plasma concentration

- Carbamazepine
- Dexamethasone
- Phenobarbital
- St. John’s wort
- Phenytoin
- Rifampin
  (IM: $C_{max} \downarrow$ by 54%; $AUC \downarrow$ by 74%)

*When administered in healthy subjects

### Substances That May Have Their Plasma Concentration Altered by Imatinib

<table>
<thead>
<tr>
<th>Substance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen/paracetamol</td>
<td></td>
</tr>
<tr>
<td>Triazolobenzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td></td>
</tr>
<tr>
<td>(eg, statins: $C_{\text{max}} \uparrow$ 2-fold; $\text{AUC} \uparrow$ 3.5-fold)</td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td></td>
</tr>
<tr>
<td>$\text{Ca}^{++}$ channel blockers</td>
<td></td>
</tr>
</tbody>
</table>

Drugs that may be ALTERED by imatinib

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Summary and Conclusions

- AEs associated with imatinib
  - Oedema, GI effects, muscle cramps, musculoskeletal pain, rash, and fatigue
  - Generally mild to moderate, often self-limited
  - Require prompt, effective management

- Management of common nonhaematological AEs
  - Can usually be managed with medications to relieve symptoms
  - Severe events may require interruption of therapy
Summary and Conclusions (cont’d)

- Common haematological AEs
  - Neutropenia, thrombocytopenia, anaemia
  - Most nonsevere (grades 1/2) and manageable

- Management of severe events
  - Interruption of therapy
  - Dose reduction
  - Growth-factor support
Summary and Conclusions (cont’d)

- Grade 3/4 liver transaminase or bilirubin elevations
  - Incidence: 3%-6%
  - Usually of limited duration
- Management options
  - Interruption of therapy
  - Dose reduction
Summary and Conclusions (cont’d)

- Compliance and persistency
  - Compliance with imatinib could be improved
  - Less than 100% adherence to antineoplastic therapy is evidence of a problem
  - Subtherapeutic imatinib dosing may lead to resistance

- Strategies for improving compliance and persistency
  - Increased monitoring of adherence
  - Aggressive management of AEs
  - Open physician-patient communications
  - Enhanced patient education