Summary

- Imatinib mesylate (Gleevec™) is a tyrosine kinase inhibitor, one of a new class of anticancer drugs called signal transduction inhibitors.

- A systematic review of case-series reports shows imatinib, when indirectly compared to conventional therapy, improves overall 12-month survival, but not surrogate outcomes, in individuals with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in myeloid-blast crisis, and accelerated phase. Surrogate outcomes, but not overall survival, were improved in chronic phase disease.

- Preliminary data from one randomized controlled trial suggest imatinib has a greater impact on surrogate outcomes compared to the combination of interferon-alpha and cytarabine in patients undergoing treatment for chronic phase Ph+ CML, however, it is not yet known whether it prolongs or improves quality of life.

The Technology

The search for a cancer cure has led to an understanding of the underlying biochemical signaling pathways responsible for cellular growth, division and death. These signals, which are activated temporarily in normal human cells, may become permanently activated in cancerous ones. A class of anticancer compounds called signal transduction inhibitors has emerged in an attempt to exploit this difference.

In the 1980s, it was suspected that a tyrosine kinase (bcr-abl) found in white (myeloid or lymphoid) blood cells containing a genetic abnormality called the Philadelphia chromosome translocation (Ph) was responsible for the stem cell disorder chronic myeloid leukemia (CML). A search for a new drug which could specifically target this defect led to the discovery of STI-571 (signal transduction inhibitor-571), or imatinib.

Regulatory Status

Both Health Canada and the US FDA have conditionally approved the use of imatinib mesylate (Gleevec™, Novartis) for the treatment of patients with Ph+ CML in blast crisis, accelerated phase or in chronic phase, after failure of interferon-alpha (IFN-α) therapy. Authorization from the European commission has also been granted.

Patient Group

CML has an incidence of one to two cases per 100,000 per year. Age-specific mortality increases from less than 0.1 per 100,000 in individuals age 0 to 14 years to over 8 per 100,000 in individuals over the age of 80.

The median age of diagnosis is between 60 and 69 years. Median survival time is four to six years and ranges from less than a year to more than 10 years.

Patients with CML usually present with symptoms such as weight loss, fatigue, malaise and fever. An elevated white blood cell count is usually present. In every case, the leukemia progresses through several distinct phases: an initial chronic phase lasting three to five years...
which is characterized by growth of myeloid cells; an accelerated phase, seen in 66% of patients and lasting two to fifteen months; and ultimately a blast crisis, lasting three to six months leading to death. During the latter two stages, Ph+ cells lose their ability to differentiate.

Current Practice

Allogeneic stem cell transplantation (allo-SCT) from matched siblings offers the greatest chance of long-term survival, with over 50% of younger recipients remaining disease-free after 10 years. Fewer than 25% of patients are eligible for this procedure, however, since the risk of complication is affected by age, stage of disease and donor compatibility.

Individuals ineligible for allo-SCT in chronic phase illness generally receive IFN-α or hydroxyurea. IFN-α prolongs survival in chronic phase CML compared to hydroxyurea but is not tolerated as well. Busulfan is rarely used as hydroxyurea has a proven greater benefit in prolonging survival. The combination of IFN-α with cytarabine was shown to be more effective than IFN-α alone in chronic phase disease.

The Evidence

Several trials of case-series design have investigated the utility of imatinib in chronic, accelerated and blast phase Ph+ CML. Overall survival data at 12 months and imatinib’s ability to reduce white blood cell and platelet counts to near-normal values for four weeks [defined as a complete hematological response (HR)] or to reduce Ph+ cells in the bone marrow to below detectable levels [defined as a complete cytogenetic response (CR)] are shown in Table 1.

A systematic review of all CML therapies concluded that when indirectly compared with conventional therapy, survival with imatinib is not improved in chronic phase CML, but improved in accelerated and myeloid-blast phase disease. Surrogate outcomes were improved in chronic phase CML but were similar in accelerated and myeloid-blast phase disease.

Several limitations in interpreting these results, including potential biases from trial design and inferences drawn from indirect comparisons between treatment regimens, are addressed by the authors. Consequently, the need to establish treatment effectiveness with randomized controlled trial (RCT) data is highlighted.

An unblinded RCT of crossover design (IRIS) trial is now evaluating the use of imatinib versus the combination of IFN-α and cytarabine (IFN-α/cyt) in patients with chronic phase CML. It is designed to assess the survival and quality of life of patients with newly diagnosed chronic phase Ph+ CML.

Interim data from the IRIS trial confirm the findings of the case-series and also of the systematic review. A larger impact on surrogate outcomes was observed after 12 months. Complete CR was observed in 68% (375/553) of imatinib recipients and 11.5% (64/553) of IFN-α/cyt recipients. Complete HR was observed in 96% (531/553) of imatinib recipients compared to 67% (371/553) of IFN-α/cyt recipients. Overall 12-month survival data and quality of life

<table>
<thead>
<tr>
<th>Trials</th>
<th>CML phase</th>
<th>Overall survival at 12 months, % population (95% CI)</th>
<th>Surrogate outcomes % population (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complete HR</td>
<td>Complete CR</td>
</tr>
<tr>
<td>Phase II</td>
<td>Chronic</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>(n=532)</td>
<td>(NR)</td>
<td>(85 to 91)</td>
</tr>
<tr>
<td></td>
<td>Accelerated</td>
<td>74</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(n=235)</td>
<td>(68 to 81)</td>
<td>(NR)</td>
</tr>
<tr>
<td></td>
<td>Myeloid-Blast</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(n=260)</td>
<td>(NR)</td>
<td>(NR)</td>
</tr>
<tr>
<td>Phase III</td>
<td>Chronic</td>
<td>NR</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>(n=1,106)</td>
<td></td>
<td>(NR)</td>
</tr>
</tbody>
</table>

HR=Complete Hematologic Response; CR=Complete Cytogenetic Response; NR=Not Reported

† Unpublished trial data may be inaccurate. The reader is cautioned against making firm interpretations based on data that have not been peer-reviewed.

‡‡ International Randomized study of Interferon versus STI-571.
data are not yet available. The interpretation of available RCT data is limited since details of trial design or analysis sufficient to support the validity of the results have not been published.

**Adverse Effects**

In the CML case-series reports, severe or life-threatening adverse effects occurred in 5, 23 and 14% of individuals in chronic, accelerated and myeloid-blast phase, respectively. In addition, 4/1,027 (0.4%, 95% CI: 0.1-1.0) individuals died as a potential outcome of therapy. Hematological adverse effects (neutropenia/leukopenia 58%, range 34-63%; thrombocytopenia 43%, range 18-60%; anemia 37%, range 6-51%) were the most common severe effects followed by edema (3%, range 1-3%), nausea and vomiting and skin rash (each 2%, range 1-3%).

Treatment interruptions and withdrawals were required in 25-40% and 1.7-5.0% of imatinib recipients, respectively, and were less common in those with chronic phase disease. The most frequent adverse effects were nausea and vomiting (62%, range 63-65%) and edema (54%, range 51-54%).

In the IRIS trial, withdrawals due to adverse events from therapy after 12 months were observed in 2% (11/553) and 6% (33/553) of imatinib and IFN-α/cyt recipients, respectively. Although these data suggest improved tolerance, they are prone to bias due to a lack of blinding. Other adverse event data have not been published.

**Rate of Technology Diffusion**

Imatinib mesylate has received much publicity because of its accelerated regulatory approval in both Canada and the US. Awareness of its novelty and perceived benefits is exceptionally high among both health professionals and consumers. This enthusiasm has led to extensive clinical investigations of imatinib for other cancers. As more trial results become available, the number of individuals eligible for imatinib may increase.

**Concurrent Developments**

Many signal transduction inhibitors are currently under investigation. Furthest along in development are the tyrosine kinase inhibitors gefitinib (Iressa™, AstraZeneca), and erlotinib (Tarceva, OSI Pharm.) and the farnesyl transferase inhibitor tipifarnib (Zarnestra™, Johnson & Johnson). Others include phenoxodiol (NV-06, Novogen Ltd.) and cetuximab (Erbitux™, ImClone).

**Implementation Issues**

The real value of imatinib therapy will be derived from its ability to prolong and improve quality of life compared to IFN-α/cyt or other conventional therapies. Although interim data for patients with chronic phase Ph+ CML show better surrogate responses compared to IFN-α/cyt after 12 months, a relationship between these outcomes and overall long-term survival has not been demonstrated. The possibility remains that patients with and without surrogate responses will survive the same length of time.

Speculating about the effectiveness of imatinib in chronic phase Ph+ CML is unrealistic without long-term RCT evidence. Several key factors, such as drug resistance and molecular remission data in the long-term are unknown. Also unknown is the impact of combining imatinib with other drugs or procedures (e.g. IFN-α, allo-SCT). Data from IRIS and other RCTs are required to characterize optimal therapeutic regimens and prove effectiveness.
References


This brief was prepared by

**Don Husereau, BScPharm, MSc; CCOHTA.**

CCOHTA takes sole responsibility for this bulletin, but we appreciate comments from the following reviewers:

**Kuljit S. Grewal, MD FRCP(C)**
Department of Medicine
Health Sciences Centre
Memorial University of Newfoundland
St. John’s, Newfoundland

**Kenneth Marshall, BA MSc MD FRCP FCFP**
Retired Professor of Family Medicine
University of Western Ontario
London, Ontario

ISSN 1488-6316 (online)
ISSN 1488-6324 (print)
Publications Agreement Number 40026386