EBS 6-15 EDUCATION AND INFORMATION 2013

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

Treatment of Chronic Myeloid Leukemia with Imatinib

Members of the Hematology Cancer Disease Site Group

A review conducted in August 2013 put Evidence Based Series (EBS) 6-15 in the Education and Information section. 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).

Evidence-based Series (EBS) 6-15 consists of three sections is available on the CCO website (http://www.cancercare.on.ca)
PEBC Hematology DSG page at:
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Section 1: Summary
Section 2: Full Report
Section 3: Guideline Review Summary and Tool

Release Date: December 12, 2013

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Treatment of Chronic Myeloid Leukemia with Imatinib
Practice Guideline Report #6-15- EDUCATION AND INFORMATION

I Walker, J Makarski, A Stevens, RM Meyer, and members of the Hematology Disease Site Group

Report Date: July 16, 2004

SUMMARY

Guideline Question
What is the role of imatinib (STI571, Gleevec™, Glivec®) in treating patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease? Outcomes of interest, in decreasing order of importance, include survival, quality of life, duration of treatment response, toxicity, hematologic response, and cytogenetic or molecular response.

Target Population
These recommendations apply to adult patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease.

Recommendations
- Imatinib is recommended as first-line therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia. The initial recommended dose of therapy is 400 mg, given orally, once daily. For patients who do not demonstrate a complete hematologic response after three months of therapy or at least a minor cytogenetic response after 12 months of therapy, the dose of imatinib should be increased to 400 mg, given orally, twice daily.

- Imatinib is recommended for patients who have become refractory to or intolerant of previous therapy (e.g., interferon +/- cytarabine, hydroxyurea) or who have disease progression to accelerated or myeloid blastic phases of the disease. For patients with accelerated or myeloid blastic phases of the disease, the starting dose of imatinib should be 600 mg, given orally, once daily with an increase in dose to 400 mg, given orally, twice daily, if an adequate hematologic or cytogenetic response is not observed.

Qualifying Statements
- The Hematology Disease Site Group considers the current evidence insufficient to make recommendations regarding the duration of imatinib therapy for those in chronic phase, whether or not they are in complete hematologic and major cytogenetic remission. It is unclear whether alternative therapy would improve the outcome of patients who have failed to attain major cytogenetic remissions or who relapse from previous remission. At present, the Hematology Disease Site Group feels that all patients taking imatinib therapy could be maintained on this therapy, with or without additional therapy, until further information becomes available. The role of additional cytogenetic monitoring, other than that performed at 12 months as per the International Randomized Study of Interferon and STI571 trial or to assist in the decision-making process for transplantation, is at present uncertain.
Eventually, failure to attain a major cytogenetic remission may become an indication for alternative or combined therapy when such therapies become established.

- For patients with chronic phase chronic myeloid leukemia who have had a hematologic and cytogenetic response to interferon (+/- cytarabine) and are tolerating this therapy, treatment decisions are more difficult. Patients should be aware of data demonstrating that, in comparison with interferon (+/- cytarabine), imatinib is associated with superior effectiveness and quality-of-life assessments and less toxicity. These benefits must be weighed against the lack of data describing the long-term effects of this medication and knowledge about potential drug resistance. The Hematology Disease Site Group considers it reasonable for physicians to recommend a change in therapy from interferon (+/- cytarabine) to imatinib, as many patients cannot remain on interferon-containing regimens long term, imatinib is associated with the benefits described above, and survival with imatinib therapy is unlikely to be inferior.

- The clinical importance of observed molecular responses in newly diagnosed patients with chronic phase chronic myeloid leukemia who achieved complete cytogenetic responses with imatinib therapy is evolving and was not addressed at this time.

- The place of bone marrow transplantation in the initial treatment of chronic myeloid leukemia has not been assessed in randomized trials. Prior imatinib therapy does not appear to compromise the results of transplantation except possibly through delays in its initiation. Patients for whom transplantation will be recommended as a second-line treatment after failure to achieve a major cytogenetic remission with imatinib should have a cytogenetic analysis testing no later than 12 months following the commencement of therapy.

- To date, the Hematology Disease Site Group has not reached consensus on the management of patients with chronic myeloid leukemia that has progressed into a lymphoid blastic phase. Preliminary results of testing imatinib in these patients have shown that any responses are usually of very short duration. The potential to use other treatments, such as regimens commonly used to treat acute lymphoblastic leukemia, should be considered.

**Methods**

Entries to MEDLINE (1985 through July 2003), PREM (last searched July 10, 2003), CANCERLIT (1985 through October 2002), and The Cochrane Library (2003, Issue 2) databases and abstracts published in the proceedings of the 1999-2003 annual meetings of the American Society of Clinical Oncology and of the 1999-2002 annual meetings of the American Society of Hematology were systematically searched for evidence relevant to this practice guideline report. In addition, the Physician’s Data Query clinical trials (http://www.cancer.gov/search/clinical_trials/), the National Guidelines Clearinghouse (http://www.guideline.gov/), and the Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) databases on the Internet were searched.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative Hematology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Hematology Disease Site Group, which comprises hematologists, medical oncologists, radiation oncologists, methodologists, and patient representatives.
External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- In total, one systematic review, one randomized controlled trial (six reports), and 12 non-randomized trials (two phase I and 10 phase II studies) were considered in the review of the evidence.

- In the randomized controlled trial reported in article form (referred to as the International Randomized Study of Interferon and STI571 study), 1106 patients with newly diagnosed chronic myeloid leukemia were randomized to receive imatinib or interferon plus cytarabine. After a median follow-up of 19 months, the group randomized to receive imatinib, in contrast to the combined therapy, had a superior rate of complete hematologic responses (95.3% versus 55.5%; p<0.001), major cytogenetic responses (85.2% versus 22.1%; p<0.001), complete cytogenetic responses (73.8% versus 8.5%; p<0.001), 18-month progression-free survival (92.1% versus 73.5%; p<0.001), and freedom from progression to accelerated or blastic phase at 18 months (96.7% versus 91.5%; p<0.001); despite these benefits, no difference in overall survival between the groups (97.2% versus 95.1%; p=0.16) has been detected to date. More grade 3 or 4 non-hematologic and hematologic toxicities were observed in patients randomized to receive interferon plus cytarabine (no statistical analysis provided). Superior QoL assessments were observed in patients randomized to receive imatinib. In patients with a complete cytogenetic response, preliminary data indicate superiority of imatinib for molecular response, the clinical significance of which is evolving and not addressed at this time.

- Imatinib has been tested in three phase II trials in patients who are refractory to or intolerant of interferon. In a trial involving 454 patients treated for a median of 17.9 months, complete hematologic responses were observed in 95% of patients and major cytogenetic responses in 60% of patients at the time of analysis. At 18 months, the estimated probability of progression-free survival was 89%, and the estimated survival was 95%. In a second trial (abstract), 194 patients followed for more than 6 months were observed to have similar complete hematologic (93%) and cytogenetic (44% major, 28% complete) responses.

- Imatinib has been tested in one phase II trial in 181 patients who have chronic myeloid leukemia in accelerated phase. The first 62 patients (34%) were initially treated with 400 mg daily, and subsequent patients were initially treated with 600 mg daily. With a median treatment duration of 10 months for patients receiving 400 mg daily and 11 months for those receiving 600 mg daily, 82% of patients had a hematologic response, with 69% being sustained for at least four weeks. The estimated duration of sustained response was greater than 12 months in 70% of patients, and estimated overall survival at 12 months was 74%. With multivariate analysis, factors most strongly predicting a longer time to disease progression were a hemoglobin of at least 100 g per litre (p=0.0002) and a starting imatinib dose of 600 mg (p=0.0005).
Imatinib has been tested in one phase I trial and two phase II trials in patients who have chronic myeloid leukemia in blastic phase. In the phase I trial, a response, defined as a complete hematologic response or a reduction in marrow blasts to 15% or less, was observed in 55% of patients with myeloid disease and 70% of patients with lymphoid disease. Of the 55% of responding patients with myeloid blastic crisis, 43% experienced a relapse at a median of 84 days of treatment (range, 42-194 days); of 70% of responding patients with lymphoid blastic crisis or Philadelphia chromosome-positive acute lymphoblastic leukemia, 86% experienced a relapse at a median of 58 days of treatment (range 42-123 days). In a phase II trial, 260 patients with chronic myeloid leukemia in myeloid blastic crisis were treated with imatinib 400 mg daily (37 patients) or 600 mg per day (223 patients). With a median duration of therapy of about four months, hematologic responses were observed in 119 patients (52%) and were sustained for four or more weeks in 70 patients (31%). Major cytogenetic responses were observed in 37 patients (16%) and were complete in 17 patients (7%). The estimated median duration of hematologic response was 10 months, and estimated median survival was 6.9 months.

Related Guidelines
Practice Guidelines Initiative's Practice Guideline Report #6-3: Drug Therapy for Chronic Myeloid Leukemia.

For further information about this practice guideline report, please contact Dr. R. Meyer, Co-Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 575-7820; FAX (905) 575-6340 or Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-4757; FAX (416) 480-6002.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:
I. QUESTION
What is the role of imatinib (STI571, Gleevec™, Glivec®) in treating patients with chronic myeloid leukemia (CML), including those with accelerated and blastic phases of disease? Outcomes of interest, in decreasing order of importance, include survival, quality of life (QoL), duration of treatment response, toxicity, hematologic response, and cytogenetic or molecular response.

II. CHOICE OF TOPIC AND RATIONALE
Chronic myeloid leukemia is a clonal disorder involving the hematopoietic stem cell and is initially manifested by the expansion in number of all myeloid cells (1). Patients commonly present with non-specific symptoms of fatigue and lethargy, with some patients also having symptoms related to anemia or splenomegaly. The disease classically progresses through three stages, referred to as chronic, accelerated (or transformed), and blastic phases. Successive phases are associated with a progressive loss of myeloid differentiation, more severe cytopenias, and an increasing number of blast cells. Median survivals in patients treated with busulfan or hydroxyurea range between three to five years (2-5); more recent trials have detected superior survival in patients treated with interferon (6). A randomized trial comparing single-agent interferon with the combination of interferon and cytarabine reported a superior survival in patients receiving combination treatment; approximately 70% of patients receiving the combination were alive at five years (7). The Practice Guideline Initiative (PGI) Hematology Disease Site Group (DSG) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC) previously published a guideline addressing treatment options for patients with CML (8), taking into account clinical studies up to and including the report of combination therapy with interferon and cytarabine.

The pathogenesis of CML involves a reciprocal translocation between chromosomes 9 and 22 (1). The Abelson (ABL) oncogene of chromosome 9, responsible for coding a tyrosine kinase protein, is translocated to a specific section of chromosome 22, referred to as the breakpoint cluster region (BCR). As a result of this 9:22 translocation, referred to as the Philadelphia chromosome, a fusion gene (BCR-ABL) is created that encodes for a novel and deregulated tyrosine kinase, which in turn is responsible for the manifestations of CML (1).

Imatinib is a new oral agent, active in CML through specific inhibition of the BCR-ABL tyrosine kinase. The drug inhibits proliferation and induces apoptosis in Philadelphia chromosome-positive cell lines as well as in fresh cells from patients with CML (1). Prescribing information (9) indicates that imatinib is well absorbed after oral administration, with maximum concentrations achieved within two to four hours post-dose. Mean absolute bioavailability is 98%. Elimination half-lives of imatinib and its major active metabolite are approximately 18 and 40 hours, respectively. The P450 enzyme, CYP3A4, is the major enzyme responsible for metabolism of imatinib, and elimination of imatinib is predominantly in the feces. The concomitant use of drugs that inhibit, induce, or are substrates for CYP3A4 may affect blood levels of imatinib; in addition, levels of these drugs may in turn be affected by the concomitant use of imatinib. No clinical studies have been conducted in individuals with hepatic or renal impairment.

Very promising preliminary data describing efficacy and toxicity outcomes for patients with CML treated with imatinib were published in 2001 (10,11) and were met with widespread publicity. As a result of these studies, imatinib was licensed in the United States on May 10, 2001 as Gleevec™ and approved for the treatment of patients with CML in blastic or accelerated phases and for those with chronic phase disease after failure of interferon therapy.
Subsequently, on December 20, 2002, and in response to the submission of data from a randomized trial (12), imatinib was approved for the first-line treatment of CML (13).

Based on emerging data describing the activity of imatinib in treating patients with CML, the Hematology DSG began a process in March 2001 to develop an evidence summary. A draft document was completed in October 2001 and was reviewed by the Policy Advisory Committee of Cancer Care Ontario. This draft was then forwarded to the Drug Quality and Therapeutics Committee of the Ministry of Health and Long-Term Care and was used to assist in the development of initial policies to reimburse imatinib through the Ministry’s Section 8 funding mechanism. Completion of the evidence summary was hindered by the repetitive reports updating a randomized trial comparing imatinib with the combination of interferon and cytarabine in previously untreated patients (12,14-16). With these results now available in article form (15,16), the Hematology DSG elected to modify criteria for including new evidence in further documents and in July 2003 completed the draft practice guideline.

III. METHODS
Guideline Development

This practice guideline report was developed by the PGI of Cancer Care Ontario’s PEBC, using the methods of the Practice Guidelines Development Cycle (17). Evidence was selected and reviewed by two members of the PGI’s Hematology DSG and methodologists. Members of the Hematology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on imatinib for the treatment of CML, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The most substantial body of evidence in this report is of mature randomized controlled trial data; therefore, recommendations by the Hematology DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

This practice guideline report describing the role of imatinib in treating patients with CML deals with a topic for which data are rapidly evolving. As a result, initial strategies used to assess the evidence available when this project was activated in March 2001 became less relevant with the subsequent reports of results from a randomized trial. Therefore, over time, the Hematology DSG has elected to alter the criteria used to assemble evidence. In this practice guideline report, the use of these different criteria is explicitly detailed.

Literature Search Strategy

MEDLINE (1985 through July 2003), MEDLINE® In-Process & Other Non-Indexed Citations (PREM; formerly known as PREMEDLINE) (last searched July 10, 2003), CANCERLIT (1985 through October 2002), and The Cochrane Library (2003, Issue 2) databases were searched. The literature search strategy is shown in Appendix I. The searches were limited to human and the English language. In addition, conference proceedings of the 1999-2003 annual meetings of the American Society of Clinical Oncology and of the 1999-2002 annual meetings of the American Society of Hematology were searched for abstracts of relevant trials. The National Guidelines Clearinghouse (http://www.guideline.gov/) and Canadian Medical
Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) databases were searched for evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Personal files were also searched.

**Inclusion Criteria**

For literature searches conducted from March 2001 to October 2002, articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with CML of any phase.
2. Phase I or II trials reporting the safety and efficacy of imatinib in patients with CML of any phase.

For literature searches conducted from November 2002 onward, articles were selected for inclusion if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with CML of any phase.
2. Systematic reviews or practice guidelines assessing imatinib in patients with CML of any phase.

**Exclusion Criteria**

For literature searches conducted from March 2001 to October 2002, reports excluded from consideration included:

1. Pilot studies describing use of imatinib in combination with other drugs.
2. Studies investigating the role of imatinib post-transplantation.

For literature searches conducted from November 2002 onward, reports excluded from consideration included:

1. Studies investigating the role of imatinib post-transplantation.

**Synthesizing the Evidence**

Because of the heterogeneity of the patient groups included in reported trials, inconsistent reporting of outcomes of interest, and varying criteria used to define outcome measures, the results of the trials were not pooled.

**IV. RESULTS**

**Part 1: March 2001 – October 2002**

**Literature Search Results**

Using the eligibility criteria that were in operation for the period of March 2001 to October 2002, 12 non-randomized trials were eligible for inclusion in this systematic review (Table 1). These trials included two phase I trials (both in article form) and 10 phase II trials (three in article form and seven in abstract form). The phase I trials reported the results of testing imatinib in patients with chronic phase CML who were either resistant to or intolerant of interferon (10) and in patients in the blastic phase of disease (11). The phase II trials reported the results of testing imatinib in patients with disease that was in early chronic (18) or chronic...
(19), accelerated (20), or blastic (21,22) phase, patients representing various phases (23,24), and in patients who were either resistant to or intolerant of interferon (25-27).

Table 1. Non-randomized studies included in this practice guideline report.

<table>
<thead>
<tr>
<th>First Author, Year (reference)</th>
<th>CML Stage</th>
<th>Criteria</th>
<th>Study Type</th>
<th># Entered / # Evaluable (%)</th>
<th>Hem.Resp. (%)</th>
<th>Cyt.Resp. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Druker, 2001, (10) b</td>
<td>Chronic</td>
<td>Resistant to or intolerant of interferon</td>
<td>Phase I</td>
<td>83 / 83 (100)</td>
<td>93</td>
<td>31 (17/54)</td>
</tr>
<tr>
<td>Druker, 2001, (11) b</td>
<td>Blast crisis or Ph-positive ALL</td>
<td>ALL: resistant to or relapsed from previous therapy</td>
<td>Phase I</td>
<td>58 / 58 (100)</td>
<td>55 (myeloid)c</td>
<td>12</td>
</tr>
<tr>
<td>Kantarjian, 2001, (18)</td>
<td>Chronic</td>
<td>Newly diagnosed</td>
<td>Phase II</td>
<td>50 / 47 (94)</td>
<td>98</td>
<td>77</td>
</tr>
<tr>
<td>Kantarjian, 2002, (19)</td>
<td>Chronic</td>
<td>Newly diagnosed</td>
<td>Not stated</td>
<td>400 vs. 800 mg At 3 mo: 50 / 49 (98) vs. 33 / 22 (67) At 6 mo: 50 / 44 (88) vs. NR</td>
<td>NR</td>
<td>400 vs. 800 mg At 3 mo: NR vs. 86% (major); 39% vs. 59% (complete) At 6 mo: 56% vs. NR (complete)</td>
</tr>
<tr>
<td>Kantarjian, 2002, (25)b</td>
<td>Chronic</td>
<td>Resistant to or intolerant of interferon</td>
<td>Phase II</td>
<td>532 / 454 (85)</td>
<td>95 (complete)</td>
<td>60</td>
</tr>
<tr>
<td>Rosti, 2001, (26)</td>
<td>Chronic</td>
<td>Resistant to or intolerant of interferon</td>
<td>Phase II</td>
<td>300d / 194 (65)</td>
<td>93 (complete)</td>
<td>44</td>
</tr>
<tr>
<td>Cortes, 2002, (27)</td>
<td>Chronic</td>
<td>Resistant to or intolerant of interferon</td>
<td>Not stated</td>
<td>34 / 21 (62)</td>
<td>100 (complete)</td>
<td>90</td>
</tr>
<tr>
<td>Talpaz, 2002, (20)b</td>
<td>Accelerated APp</td>
<td>Phase II</td>
<td>235 / 181 (77)</td>
<td>82</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Sawyers, 2002, (21)b</td>
<td>Blast crisis BPp</td>
<td>Phase II</td>
<td>260 / 229 (88)</td>
<td>52</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Kantarjian, 2002, (22)b</td>
<td>Blast crisis BPfp</td>
<td>Phase II</td>
<td>75 / 75 (100); nonlymphoid, n=65</td>
<td>23</td>
<td>4 (complete)</td>
<td></td>
</tr>
<tr>
<td>Hochhaus, 2002 (23)</td>
<td>Various phases (late chronic, accelerated, blast)</td>
<td>NR</td>
<td>Not stated</td>
<td>300 / 299 (99.7)</td>
<td>NR</td>
<td>18 (complete)</td>
</tr>
<tr>
<td>Rendo, 2002, (24)</td>
<td>Various phases (chronic, accelerated, blast)</td>
<td>CP = resistant, relapsed, or intolerant of IFN</td>
<td>Not stated</td>
<td>147 / 139 (95)</td>
<td>CP: 87.7% AP: 89.5% BP: 61% (overall response)</td>
<td>CP: 48.6% AP: 14.3% BP: 11.8% (complete)</td>
</tr>
</tbody>
</table>

Note: CML=chronic myeloid leukemia; Hem.Resp.=hematologic response; Cyt.Resp.=major cytogenetic response; mo=months; nonlymphoid=myeloid or undifferentiated; NR=not reported; Ph-positive ALL=Philadelphia chromosome positive acute lymphoblastic leukemia; vs.=versus.

a For outcomes reported in this table.
b Published in full.
Outcome defined as a complete hematologic response or a reduction in marrow blasts to 15% or less.

Used as an estimate because more than 300 patients were enrolled (exact value not provided).

AP=accelerated phase, defined as the presence in blood or marrow of at least 15% to less than 30% blasts or at least 30% blasts plus promyelocytes (as long as <30% blasts present), at least 20% basophils in peripheral blood, or platelet counts less than $100 \times 10^9/L$ unrelated to anticancer therapy (28).

BP=30% or more blasts in blood or marrow or presence of extramedullary disease other than liver or spleen enlargement.

BP=at least 30% blasts in blood or marrow.

One randomized trial, reported in abstract form, compared imatinib with the combination of interferon and cytarabine in patients with early-stage disease (14). As this trial has been subsequently reported in article form (15,16), the results will be described in Part 2 of this section.

Sources of funding for all of these studies was examined. In the majority of studies, a pharmaceutical company sponsored the trial (10[in part],11[in part],12,14-16,19-21,26,29-34) or formed part of the authorship (22-24); in two studies (18,27) no information on funding was provided.

Phase I Studies

Newly Diagnosed CML

No phase I studies were identified.

CML Resistant to, or Patients Intolerant of, Interferon Therapy

Druker et al. (10) published a phase I study testing imatinib in 83 patients with chronic phase CML who were either resistant to or intolerant of interferon. The primary objective of this study was to assess the safety and tolerability of imatinib; a secondary objective was to assess anti-leukemic activity. The study design included 14 successive dose cohorts who were prescribed imatinib at doses ranging from 25 to 1000 mg per day. Outcomes of toxicity and hematologic and cytogenetic responses were predefined; toxicity was graded using the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC). In addition, pharmacokinetic studies and BCR-ABL tyrosine kinase inhibition were assessed.

Imatinib was generally well tolerated; two patients receiving doses of 300 mg or more discontinued therapy because of angina recurrence (the patient had a history of coronary artery disease) and skin rash, respectively. Grades 1 and 2 toxicities were common and included nausea, diarrhea, and dyspepsia. Grades 3 and 4 toxicities were rare and dose related (Table 2). No treatment-associated deaths were observed, and the authors did not identify a maximum tolerated dose.

Table 2. Percentage of patients experiencing NCI-CTC grades 3 or 4 toxicities in a phase I trial testing imatinib in patients with chronic phase chronic myeloid leukemia who are resistant to or intolerant of interferon.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>25-140 mg n=14</th>
<th>200-300 mg n=23</th>
<th>350-500 mg n=18</th>
<th>600-1000 mg n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: NCI-CTC=National Cancer Institute Common Toxicity Criteria; n=number.
Hematologic responses, defined as a 50% reduction in white cell count from baseline, for 2 weeks or more, were observed in 77 patients (93%), including all 73 patients who received doses of at least 140 mg per day. Complete hematologic responses (CHR), defined as a reduction in white cell count to less than 10,000/mm$^3$ and platelet count to less than 450,000/mm$^3$, for at least four weeks, were observed in 64 patients (77%), including 53 of 54 patients (98%) who received at least 300 mg per day. Major cytogenetic responses, defined as a reduction in Philadelphia chromosome expression to 0-35% of cells, were observed in 31% of patients receiving at least 300 mg per day, with no dose effect when visually examining response rates across dose groups. Pharmacokinetic data demonstrated a plasma half-life of 13-16 hours, and the mean plasma trough level 24 hours after a dose of 400 mg at steady state exceeded the concentration required for in vitro inhibition of cellular phosphorylation by BCR-ABL and death of BCR-ABL–positive cell lines. Inhibition of tyrosine phosphorylation of CRKL, a major substrate of BCR-ABL, occurred with a plateau at daily doses of 250-750 mg.

**CML in Accelerated Phase**

No phase I studies were identified.

**CML in Blastic Phase**

Druker et al. (11) published a phase I study testing imatinib in 58 patients with CML in myeloid (n=38) or lymphoid (n=10) blast phase (defined as more than 30% blasts in marrow or blood) or with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) that was resistant to or had relapsed from previous therapy (n=10). The study’s objectives were to assess the anti-leukemic activity and safety of imatinib. The study design included successive dose cohorts of six to eight patients who were prescribed imatinib at doses ranging from 300 to 1000 mg per day. Imatinib was generally well tolerated. The most common side effects included nausea (55% of patients), vomiting (41%), and edema (41%), with most of these being of grade 1 or 2 severity. Grades 3 and 4 toxicities (Table 3) were less common. Grade 4 neutropenia and thrombocytopenia occurred in 40% and 33% of patients, respectively. No deaths were attributed to imatinib.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grades 3 or 4 only</th>
<th>300 mg/day n=8</th>
<th>400-500 mg/day n=17</th>
<th>600-1000 mg/day n=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>76</td>
<td>76</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63</td>
<td>64</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Note: NCI-CTC=National Cancer Institute Common Toxicity Criteria; n=number of patients assigned to these dose cohorts.

A response, defined as a CHR or a reduction in marrow blasts to 15% or less, was observed in 55% of patients with myeloid disease and 70% of patients with lymphoid disease. A complete hematologic remission was observed in eight patients (14%). Major cytogenetic responses were observed in seven patients (12%). Responses were often short, particularly in patients with lymphoid disease: of the 55% of responding patients with myeloid blastic crisis, 43% experienced a relapse between 42 and 194 days of treatment (median, 84 days), and of
70% of responding patients with lymphoid blastic crisis or Ph+ ALL, 86% experienced a relapse after a median of 58 days of treatment (range 42 to 123 days).

**CML in various phases**
No phase I trials were identified.

**Phase II Studies**

**Newly Diagnosed CML**

Kantarjian et al. reported in abstract form (18) the preliminary results of therapy with imatinib, 400 mg per day, in 47 newly diagnosed patients in early chronic phase. Median follow-up was four months. CHRs (98%) and three-month cytogenetic responses (77% major, 36% complete) were observed. These cytogenetic responses were more frequent than that observed in historical cohorts treated with interferon-containing regimens also evaluated at three months.

Kantarjian et al. reported in abstract form (19) the results of two studies of imatinib 400 mg daily (n=50) and 800 mg daily (n=33), respectively. Authors did not indicate whether the trial was phase I or II. Authors compared the results (n=29 and n=22, respectively) with an undescribed group receiving interferon regimens (n=274). Complete cytogenetic response was significantly higher with imatinib than interferon (no statistical analysis provided); imatinib data are shown in Table 1 (interferon: 0% at 3 months; 3% at 6 months). Authors also stated that major cytogenetic response was significantly higher with imatinib than interferon, but only data for the 800 mg group are provided. There was a slightly higher occurrence of manageable toxicities in the 800 mg group at 3 months (no statistical analysis provided).

**CML Resistant to, or Patients Intolerant of, Interferon Therapy**

Kantarjian et al. (25) have reported the results of an international phase II study testing imatinib in 532 patients with chronic phase CML. Four hundred and fifty-four patients had the diagnosis confirmed by central review and formed the study cohort; of these, 29% had hematologic resistance to interferon, 35% had cytogenetic resistance, and 35% were intolerant. The primary efficacy outcome was to determine the rate of major cytogenetic response observed with imatinib when given at doses of 400 mg daily; secondary efficacy outcomes were the rate of CHR, time to progression (progression-free survival [PFS]), and overall survival. The median duration of treatment was 17.9 months (range 0.5 to 20.3). At the time of analysis, CHRs in 430 patients (95%) and major cytogenetic responses in 272 patients (60%) were observed. Of those with major cytogenetic responses, complete cytogenetic responses were observed in 188 patients (69%; 41% of the study cohort). Major cytogenetic responses were maintained in 228 (84%) patients, but in 44 (16%) patients, major cytogenetic responses were lost. At 18 months, the estimated probability of PFS (progression to accelerated or blastic phase, treatment discontinuation because of unsatisfactory effect, or death) was 89%, and estimated survival was 95%. Progression-free and overall survivals were similar in the subgroups of patients who were eligible for inclusion because of hematologic failure, cytogenetic failure, or intolerance with previous interferon therapy (no statistical analysis provided). The occurrence of a major cytogenetic response at three months was associated with higher PFS (p=0.005). Safety analyses were conducted in all 532 patients. Serious, therapy-related adverse effects occurred in 29 patients (5.5%), and therapy-related adverse effects caused the withdrawal of 11 patients (2.1%). Non-hematologic adverse effects were mostly mild (grade 1 or 2). Serious hematologic adverse effects consisted mainly of neutropenia (35%) and thrombocytopenia (20%).

A second phase II study (26), similar in design to the international study above, has been initiated by the Italian Cooperative Study Group on CML. Of over 300 patients entered, 194 who had been followed for more than 6 months have been analyzed (study opened August
Similar to the international study, frequent rates of complete hematologic (93%) and cytogenetic (44% major, 28% complete) responses were observed. As in the international study, therapy was well tolerated, with only 11 patients discontinuing therapy because of adverse effects, treatment failure, or other reasons.

Cortes et al. (27) have reported the results of testing imatinib, 800 mg daily, in 34 patients intolerant of, with anticipated intolerance of, or resistant to interferon. Authors did not indicate whether the trial was phase I or II. All the 21 patients treated for 3 months or more included in the analysis had a CHR. At three months, 19 (90%) had a major cytogenetic response, and 15 (71%) were complete. Toxicity resulted in dose reductions in 12 patients (six patients because of hematologic toxicity). Most common grade 3 or higher non-hematologic toxicities were skin (three patients), fatigue (one patient), cramps (one patient), and abnormal liver function (one patient).

**CML in Accelerated Phase**

Talpaz et al. (20) have reported the results of a phase II study evaluating imatinib in 235 enrolled patients with CML in accelerated phase; 181 patients (77%) were accepted as eligible. Accelerated phase was defined as: 15% to less than 30% blasts in marrow or peripheral blood; at least 30% blasts plus promyelocytes in bone marrow or blood (as long as less than 30% blasts were present); basophilia of at least 20% in blood; or thrombocytopenia of less than 100 x 10^9 platelets per litre unrelated to therapy.

The primary aims of this study were to determine the rate of sustained hematologic response, lasting at least four weeks, and the toxicity of treatment. Hematologic response was defined as CHR, marrow response, or return to chronic phase. A CHR was defined as a reduction in myeloblast cells in the marrow to less than 5%, no myeloblasts in blood, neutrophil count of at least 1.5 x 10^9 per litre, platelet count at least 100 x 10^9 per litre, and no evidence of extramedullary disease involvement. Secondary end points were the induction of cytogenetic response, duration of hematologic response, time to disease progression, and overall survival.

The first 62 of the 181 eligible patients (34%) were initially treated with 400 mg daily, and subsequent patients were initially treated with 600 mg daily. After a median treatment duration of 10 months for patients receiving 400 mg daily and 11 months for those receiving 600 mg daily, hematologic responses were seen in 82% of 181 eligible patients, with 69% of 181 patients being sustained for at least four weeks. Sustained responses were similar between dose groups and were assessed as complete in 34% of eligible patients. The estimated median duration of sustained response was 13.4 months in the 400 mg dose group and was not reached in the 600 mg dose group at the time of analysis. The estimated duration of sustained hematologic response was greater than 12 months in 70% of patients, including 57% of those in the 400 mg group and 79% in the 600 mg dose group. Major cytogenetic responses occurred in 24% of patients. The median time to disease progression was 8.8 months for patients in the 400 mg group and had not been reached for patients in the 600 mg group at the time of analysis. Median overall survival had not been reached at the time of analysis; estimated overall survival at 12 months in the 400 mg and 600 mg groups was 65% and 78%, respectively, and was 74% for all eligible patients. With multivariate analysis, factors most strongly predicting a longer time to disease progression were a hemoglobin of at least 100 g per litre (p=0.0002) and a starting imatinib dose of 600 mg (p=0.0005).

The most common adverse effects among all enrolled patients were nausea, vomiting, diarrhea, edema, skin rash, and muscle cramps; a number of grades 1 and 2 adverse effects were more common with the 600 mg dose, but the incidence of grades 3 and 4 toxicities were similar in both dose groups (statistical analysis not provided). Grades 3 or 4 neutropenia occurred in 58% of enrolled patients and thrombocytopenia in 43%, being similar with both doses (statistical analysis not provided). Overall, most adverse effects were of grades 1 or 2 severity, and imatinib was well tolerated, with only six patients (600 mg dose group) withdrawing
because of drug-related adverse events. One death, due to liver failure, was observed in a patient who had previously undergone bone marrow transplantation and was ascribed to a possible interaction between imatinib and acetaminophen.

**CML in Blastic Phase**

Sawyers *et al.* (21) have published the results of a phase II study testing imatinib in 260 patients with CML in myeloid blastic crisis conducted by the International Gleevec Study Group. The diagnosis of blast cell crisis was confirmed on central review in 229 patients forming the group for efficacy analysis. The patients were treated with imatinib, initially at a daily dose of 400 mg (37 patients) or later with 600 mg (223 patients). The objectives were to determine the rate of sustained hematologic response (CHR, marrow response, or return to chronic phase) lasting four weeks or more and safety. Secondary efficacy outcomes were cytogenetic response, duration of hematologic response, and overall survival. The median duration of therapy for all enrolled patients was 3.7 months in the 400 mg dose group and four months in the 600 mg dose group. Hematologic responses on one occasion or more were observed in 119 patients (52%), and sustained hematologic responses for four or more weeks occurred in 70 patients (31%). A CHR was observed in 35 patients (15%). A major cytogenetic response (0% to 35% Ph+ cells) was observed in 37 patients (16%) and was complete in 17 patients (7%). In patients with sustained hematologic response, the estimated median duration of hematologic response was 10 months. The estimated median survival was 6.9 months, and estimated survival was 20% at 18 months. By multivariate analysis, platelet count of 100 x 10^9 per litre or more and peripheral blood blast level less than 50% predicted for longer survival (p<0.001). Among all enrolled patients, non-hematologic toxicities were mainly grades 1 or 2, but grades 3 or 4 hematologic toxicities were common (neutropenia, 63%; thrombocytopenia, 62%). Thirteen patients (5%) discontinued therapy for various drug-related toxicities including neutropenia, pancytopenia, dermatitis/rash, gastrointestinal effects, cardiac failure, and edema. One suspected drug-related death occurred (death from renal and cardiac failure).

Kantarjian *et al.* (22) published a phase II study evaluating imatinib in 75 patients with Ph+ CML in lymphoid (n=10) or myeloid/undifferentiated (n=65) blastic phase. Imatinib doses ranged from 300 to 1000 mg per day. Data were analyzed at a median follow-up of 11 months. Of patients with myeloid or undifferentiated disease, 15 (23%) had a CHR, 11 (17%) had hematologic improvement (HI), six patients (8%) returned to second chronic phase, and one patient with extramedullary disease had a complete response. Of patients with CHR or HI, 11 (42%) had a cytogenetic response, and four of those were complete. Of patients with lymphoid disease, one (10%) had a CHR, one had a HI (10%), and one (10%) returned to second chronic phase. Only the patient with CHR had a cytogenetic response, which was complete. The estimated median durations of the hematologic and cytogenetic responses were 4.5 and 3.3 months, respectively (data extracted from published curves). Median survival was 6.5 months for patients with myeloid/undifferentiated disease and was 7 months for patients with lymphoid disease. In the multivariate analysis, excluding patients who died before eight weeks, the treatment response at eight weeks was an independent prognostic factor for survival (p<0.05). Non-hematologic toxicities were mainly grades 1 or 2, with nausea/vomiting and liver dysfunction being the most common (47% of patients each). Among patients with pretreatment granulocyte counts greater than 1x10^9 per litre and platelet counts 100x10^9 per litre or greater, a decrease in granulocyte count to less than 0.5x10^9 per litre occurred in 24 of 48 patients (50%) and a decrease in platelet counts to less than 50x10^9 per litre in 15 of 34 patients (44%). Febrile episodes occurred in 13 patients (17%). No deaths were attributed to imatinib use. When comparing patients with myeloid/undifferentiated disease with a historical cohort (n=133) similar in characteristics except for age (historical cohort was younger), objective response rates (including CHR, HI, partial hematologic response, and return to second chronic phase) and
median survival were superior with imatinib (55% versus [vs.] 29% [p=0.001] and 7 vs. 4 months [p=0.04], respectively).

CML in Various Phases
Hochhaus et al. reported in abstract form (23) a study of 300 patients with BCR-ABL–positive CML in late chronic (n=135), accelerated (n=86), or blastic (n=78) phase. The authors did not indicate whether the trial was phase I or II. Imatinib was given in a range of 400 to 800 mg daily. The median treatment duration was 260 days, with a maximum follow-up time of 850 days. Fifty-five patients obtained complete cytogenetic remission, and all remained positive for BCR-ABL transcripts after a median follow-up of 1.3 years.

Rendo et al. reported in abstract form (24) a study of 147 patients with CML in different phases, either in chronic phase but resistant, relapsed, or intolerant to interferon (n=58), in accelerated phase (n=53), or in blastic phase (n=36); data were reported for 57, 48, and 34 patients, respectively. The authors did not indicate whether the trial was phase I or II, so phase II was inferred. Imatinib was given at an initial dose of 400 mg daily for chronic phase and 600 mg daily for the accelerated and blastic phases. The following outcomes are reported in the order of chronic, accelerated, and blastic phases, respectively. A CHR was observed in 87.7%, 68.7%, and 26%, respectively, and an overall hematologic response occurred in 87.7%, 89.5%, and 61%, respectively. A complete cytogenetic response was observed in 48.6%, 14.3%, and 11.8%, respectively. Toxicities (hematologic, edema, nausea, vomiting, and skin rash) were mostly in patients in accelerated or blastic phase. Severe toxicity in 21 patients (17 in accelerated or blastic phase) resulted in the suspension of treatment in those patients.

Phase III Studies
Newly Diagnosed CML
The most important study of patients with newly diagnosed CML is the International Randomized Study of Interferon and STI571 (IRIS) comparing imatinib with the combination of interferon and cytarabine. IRIS was initially identified in abstract form (14), but later updated after November 2002; results are discussed in Part 2 of this section.

Literature Search Results
Using eligibility criteria that were in operation from November 2002 onward, nine reports (12,15,16,29-34) of one randomized controlled trial (IRIS) and one report of a systematic review (35) met the eligibility criteria for inclusion in this practice guideline report; those reports dealt only with newly diagnosed CML. The data from six IRIS reports (15,16,30,32-34) are discussed here. Full reports for IRIS were published on effectiveness and toxicity (15) and QoL (16); QoL data were subsequently updated in abstract form (30). Two additional full reports of the IRIS trial (29,31) that were not peer-reviewed were unavailable during the review of the evidence but will be reviewed when available in full. The systematic review (35) and accompanying technology assessment (36) were completed by the British National Health Service National Institute for Clinical Excellence (NICE).

Phase III Studies
Newly Diagnosed CML
The IRIS trial is a randomized comparison of imatinib with the combination of interferon and cytarabine in newly diagnosed patients (15). The randomization method was not provided in the report, and it is unclear whether allocation was concealed. Between June 2000 and January 2001, 1106 patients were recruited from 177 centers in 16 countries. Eligible patients had Ph+ CML in chronic phase, were within six months of diagnosis, and had received no treatment for CML other than hydroxyurea or anagrelide. Patients were randomized to receive
imatinib 400 mg orally daily or a combination of interferon (doses escalated to 5 million U/m² per day, subcutaneously) and cytarabine (20 mg/m² per day, subcutaneously, for 10 days per month). The imatinib dosage could be increased to 800 mg daily if a CHR was not observed at three months or at least a minor cytogenetic response was not observed at 12 months. Patients could be crossed over to the alternate treatment arm in the event of a lack of response, loss of response, increase in white cell count, intolerance of treatment, or an adverse effect determined to be immediately life-threatening. The primary endpoint was PFS, defined as death, development of accelerated or blastic phase disease, loss of a CHR, loss of major cytogenetic response (increase in Ph+ cells by 30 percentage points or more on two cytogenetic analyses at least one month apart), or an increasing white blood cell count in patients without a CHR. The study was analyzed by intention to treat (ITT), based on initial treatment allocation; for PFS, patients were analyzed by ITT regardless of crossover, and for other efficacy outcomes, patients were analyzed until crossover or discontinuation. Patient characteristics were balanced between treatment arms with respect to median age, gender, time since diagnosis, Hasford (Euro) and Sokal risk groups, hematologic parameters, and spleen size at least 10 cm below costal margin. Additional chromosome abnormalities were more common in patients randomized to imatinib (12.1% vs. 7.6%; p=0.015).

Median follow-up at the time of analysis was 19 months. The median dose of imatinib was 400 mg per day (range 114 mg to 732 mg), while that of interferon was 4.8 million U per day (range 0.6 million U to 11.3 million U). Of those randomized to receive cytarabine, 28.8% did not receive this agent, but for those who did receive it, the median number of courses given was 4 (range 1 to 23). Information on treatment status at the time of analysis is briefly outlined in Table 4.

### Table 4. Treatment status in IRIS at a median follow-up of 19 months.

<table>
<thead>
<tr>
<th>Treatment status</th>
<th>Number of patients (% of those randomized)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imatinib (n=553 randomized)</td>
</tr>
<tr>
<td>Still receiving allocated therapy</td>
<td>474 (85.7%)</td>
</tr>
<tr>
<td>Discontinued allocated therapy</td>
<td>68 (12.3%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Cross-over to other arm</td>
<td>11 (2.0%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Intolerance or reluctance to continue</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>allocated therapy</td>
<td></td>
</tr>
</tbody>
</table>

Note: IFN=interferon; n=number.  
*Subcategories of events do not sum to total for the category because not all subcategories in original paper are provided here.

Responses to therapy were superior in patients randomized to receive imatinib. Compared with those in the interferon plus cytarabine group, the imatinib group had superior CHR and major and complete cytogenetic responses, a more rapid occurrence of major cytogenetic responses (response after three months), and superior 18-month freedom from progression to accelerated or blastic phase and 18-month PFS (Table 5). Visual inspection of curves revealed a similar PFS among different Sokal risk groups in the imatinib arm, while there was a slight divergence in PFS among risk groups in the interferon plus cytarabine arm (not assessed statistically), as expected from previous studies. Overall, PFS was longer in patients randomized to imatinib in comparison with interferon plus cytarabine (p<0.001), regardless of risk categorization. No difference in overall survival between the randomized groups was detected (Table 5).
Table 5. Outcomes of the IRIS trial.

<table>
<thead>
<tr>
<th>Outcome at median follow-up of 19 months (except where noted)</th>
<th>Percentage of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (n=553)</td>
<td>IFN+cytarabine (n=553)</td>
<td></td>
</tr>
<tr>
<td>Complete hematologic response (CHR)</td>
<td>95.3%</td>
<td>55.5%</td>
</tr>
<tr>
<td>Major cytogenetic response</td>
<td>85.2%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Complete cytogenetic response</td>
<td>73.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic response at 3.5 mo</td>
<td>58%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Progression-free survival at 18 mo</td>
<td>92.1%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Freedom from progression to AP or BP at 18 mo</td>
<td>96.7%</td>
<td>91.5%</td>
</tr>
<tr>
<td>Overall survival at 18 mo</td>
<td>97.2%</td>
<td>95.1%</td>
</tr>
</tbody>
</table>

Note: AP= accelerated phase of disease; BP=blastic phase of disease; IFN=interferon; mo=months; n=number of patients randomized.

<sup>a</sup>Fisher exact test.

<sup>b</sup>Estimated from Kaplan-Meier curve.

<sup>c</sup>Log-rank test.

Toxicity evaluations were based on 551 and 553 patients in the imatinib and combination therapy groups, respectively. Among the non-hematologic toxicities, more grade 3 or 4 toxicities were observed in patients randomized to receive interferon plus cytarabine (no statistical analysis provided) than in patients randomized to imatinib; notable differences were seen in nausea (5.1% vs. 0.7%, respectively), fatigue (24.4% vs. 1.1%), joint pain (7.3% vs. 2.4%), myalgias (8.1% vs. 1.5%), and depression (12.8% vs. 0.4%). More grade 3 or 4 neutropenia (25% vs. 14.3%) and thrombocytopenia (16.5% vs. 7.8%) were also observed with interferon plus cytarabine (no statistical analysis provided).

The IRIS study included QoL assessments that have been reported separately (16). Quality of life was assessed using the Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) and the European Quality of Life Questionnaire-5D (EuroQoL-5D) indices. Patients assessed their own QoL by using a questionnaire. Blinding was not possible in that study due to the nature of the administration of the regimens. The FACT-BRM is a validated instrument that includes 40 questions, tests multiple domains that contribute to quality of life, and has been translated into multiple languages. From that index, a subset of 27 questions (physical, functional, and treatment-specific subscales) was selected to create a Trial Outcome Index (TOI), which forms the primary outcome measure of this analysis; it is unclear if the TOI is validated. The FACT-BRM index instrument was completed prior to therapy, monthly for six months, and after nine and twelve months of therapy. The primary analysis was by ITT, with 95% of randomized patients included in the analysis, and specific secondary analyses were performed to deal with crossovers. Analyses accounted for missing data and dropouts. In the ITT analysis, the imatinib group had significantly higher mean TOI scores beginning with the one-month post-therapy assessment and continuing with each of the subsequent assessments (p<0.001 for all assessments). The major contribution to that difference was a decline in scores in the interferon plus cytarabine group at the one-month post-therapy assessment (greatest difference between arms visually at that timepoint), with a gradual increase in the scores of patients assigned to interferon plus cytarabine after the second month, although a significant difference between groups remained at 12 months (p<0.001). Similar superior results in patients randomized to receive imatinib were observed in the assessments of the other domains of the FACT-BRM (social or family well-being [p<0.05 for most assessments; p=0.046 at 12 months], emotional well-being [p<0.05 for all assessments]) and with use of the EuroQoL-5D instrument (p<0.001 for all post-baseline assessment timepoints). In the abstract
update of that study (30), 18-month QoL by ITT detected significantly decreased mean TOI scores on interferon plus cytarabine (n=519) compared with imatinib (n=530) (p<0.001).

In the secondary analysis evaluating treatment crossover, the mean TOI scores of patients randomized to receive interferon plus cytarabine improved after crossing over to receive imatinib, whereas the scores for patients remaining on the initially assigned treatment did not appreciably change (16). At 12 months, there was no difference in mean TOI scores between patients initially randomized to imatinib and those assigned to interferon plus cytarabine who crossed over to imatinib (p=0.088). Significant improvement in mean TOI scores were observed at the 12-month assessment in patients crossing-over from interferon plus cytarabine to imatinib compared with those who remained on their initial assignment to interferon plus cytarabine (p<0.001). In the abstract update (30) of the QoL full report, patients initially allocated to interferon plus cytarabine who crossed over to imatinib (n=261) continued to show superior mean TOI scores at 18 months (p<0.001), but it is unclear whether both the imatinib (n=519) and combination treatment (n=258) groups receiving treatment as allocated were included in the analysis or whether separate analyses were conducted with each group.

Preliminary molecular response data from patient subsets of the IRIS trial have been published in abstract form (32-34). In one report (32), 313 patients with a complete cytogenetic response (imatinib, n=284; combination therapy, n=29) were included in the analysis, but more patients on imatinib than combination therapy (40% vs. 7%, no statistical analysis provided) had at least three evaluations after cytogenetic response because of more rapid occurrence of complete response. Imatinib was superior to combination therapy for molecular response six months after complete cytogenetic response (median log reduction from baseline in the ratio of BCR-ABL to BCR levels; p=0.03) and when analyzed at 12 months after trial initiation (percent of patients with >3 log reduction; p=0.004). Although the two other reports (33,34) also showed significant results, smaller patient subsets were analyzed and important differences exist in how analyses were conducted among the reports. In addition, similar molecular responses between first-line imatinib and imatinib by crossover were reported (33,34).

In summary, the IRIS trial demonstrates that in comparison with interferon plus cytarabine, treatment with imatinib is associated with superior hematologic and cytogenetic responses, PFS, and freedom from accelerated or blastic phase disease. Treatment with imatinib is better tolerated with fewer toxicities reported, less common cessation of therapy due to intolerance or reluctance to continue, and superior scores in QoL assessments. Patients assessed their own QoL by using a questionnaire. Blinding was not possible in that study due to the nature of the administration of the regimens. The superior outcomes are based on ITT analyses that include subsequent improvements in multiple outcome measures in patients initially assigned to receive interferon plus cytarabine who later benefited from crossing over to receive imatinib.

**Systematic Review**

The NICE has completed a systematic review (35) and accompanying technological assessment (36) of imatinib in the treatment of CML. That body constitutes a Special Health Authority for England and Wales and is accountable to the United Kingdom National Health Service. Based on data that are largely described in Part 1 of the Results section of this practice guideline report, NICE issued a recommendation in September 2002 indicating that imatinib was recommended as an option for treating patients with CML who were refractory to or intolerant of interferon or who had accelerated or blastic phase disease. No recommendation was provided with respect to initial therapy; the document was completed prior to the availability of the IRIS randomized trial results.

With the availability of results from the IRIS trial, NICE has updated their evaluation (36); as of June 2003, preliminary recommendations have been reached, and a consensus process
to finalize these recommendations is in process. The new preliminary recommendations include:

1. Imatinib is recommended as first-line treatment in the management of people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in the chronic phase.

2. Imatinib is recommended as an option for the treatment of people with Philadelphia-chromosome-positive CML in the accelerated phase or in blast crisis provided they have not received imatinib treatment at an earlier stage.

3. For people in chronic-phase CML currently receiving interferon alfa (IFN-α) as first-line treatment, the choice of whether to change to imatinib should be informed by the response of the disease to current treatment and by the tolerance of the patient to IFN-α. This decision should be made after informed discussion between the patient and the responsible clinician, taking full account of the evidence on the risks and benefits of imatinib and the wishes of the patient. (36)

These recommendations were based on evidence that overlaps with that described in this practice guideline report, and are largely influenced by the results of the IRIS trial. Only the first recommendation is based on evidence from the systematic review; the latter recommendations are not.

In addition, NICE completed an economic evaluation (36) in their technology assessment report, not based on systematic review methodology. NICE concluded that, in comparison with interferon, first-line treatment with imatinib would result in an incremental cost-effectiveness ratio (ICER) of about £26,000 (range £13,500-£52,000) per quality-adjusted life year (QALY). Comparison values provided for perspective included ICERs of £87,000 per QALY when first-line therapy with imatinib was compared with hydroxyurea and over £1,000,000 per QALY when first-line therapy with interferon was compared with hydroxyurea.

V. INTERPRETATION AND CONSENSUS

The development of imatinib has been based on a sound understanding of the molecular pathogenesis of CML and a rational process of determining how that process might be pharmacologically altered. The results of testing imatinib in patients with CML reinforce the concept that drugs designed to specifically target key steps in the molecular pathogenesis of a malignancy may be associated with anti-tumour effects, while minimizing toxicity to other tissues. The Hematology DSG considered the available data to represent an important advance in treating patients with CML, and the DSG’s interpretation of the role of imatinib evolved as new data emerged from testing this medication in various situations and with different trial designs.

Based on data reported in Part 1 of the Results section, the following initial conclusions of the DSG that were reached in May 2002 remain valid given the data that have become available since that time:

1. Doses greater than 400 mg per day do not appear to be necessary in patients with chronic phase CML; patients in accelerated or blastic phase may benefit from an increase to 600 mg daily.

2. Imatinib is well tolerated at a dose of 400 mg daily with no more than mild or moderate (NCI-CTC grades 1 or 2) toxicities in the vast majority of patients. These toxicities are predominantly gastrointestinal (nausea, diarrhea, and dyspepsia). Other toxicities include...
fatigue, edema, myalgias, arthralgias, mild neutropenia, and thrombocytopenia; the latter hematologic toxicities are more common in patients in the accelerated or blastic phase of the disease. Life-threatening side effects (grade 4) are rare. There are no reports evaluating long-term toxicities.

3. In patients with chronic phase CML who are refractory to or intolerant of interferon, imatinib induces hematologic responses in more than 90% of patients, with complete responses seen in more than 75% of patients. Major cytogenetic responses are observed in more than 40% of patients.

4. In patients with accelerated phase CML, imatinib induces hematologic responses, with preliminary data indicating that sustained response rates may be more than 60%. The optimal starting dose may be 600 mg, rather than the 400 mg used in chronic phase patients, according to a multivariate analysis examining factors predicting response. The duration of hematologic and cytogenetic responses and impact on patient survival are unknown at this time.

5. In patients with myeloid blastic phase CML, imatinib induced hematologic responses in 52% of patients in one trial, with the responses being sustained for four weeks or more in 31% of patients. In a second study, imatinib induced hematologic responses in 55% of patients. Major cytogenetic response rates were 16% and 12% in the two trials, respectively. Data regarding dosing suggest that the optimum dose is 600 mg per day. While the duration of hematologic and cytogenetic responses and the impact on patient survival remain unknown at this time, preliminary data suggest that these responses are likely to be of less than six months duration. Median survival in the international study is 6.9 months, with the long-term survival of living patients being unknown.

With the availability of data from the IRIS trial (15,16,30-34), the role of imatinib in treating patients with newly diagnosed CML has been clarified. The trial detected that in comparison with interferon plus cytarabine, treatment with imatinib is associated with superior hematologic and cytogenetic responses and superior disease control over time, including a reduced risk of developing accelerated or blastic phase disease, and is better tolerated, with less treatment-related toxicity and cessation of therapy due to intolerance or reluctance. Finally, superior scores in patient self-assessed QoL assessments were observed. Those superior outcomes are based on appropriate, but conservative, ITT analyses that may minimize the superiority of imatinib, as patients initially assigned to receive interferon plus cytarabine later benefited from crossing over to receive imatinib. While no differences in overall survival have been detected to date, the superior outcomes in the intermediate outcome measures assessing effectiveness suggest that imatinib may be associated with superior survival and is unlikely to be associated with inferior survival. The detection of differences in overall survival in the randomized comparison of imatinib with interferon plus cytarabine may be confounded by the effectiveness of imatinib observed in patients who crossed over to that therapy.

Preliminary molecular data indicate that a superior molecular response was observed in patients treated with imatinib who achieved a complete cytogenetic response. The clinical importance of those data is evolving and not addressed at this time.

VI. ONGOING TRIALS
The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials.
The Hematology DSG is also aware of plans to develop a North American Intergroup phase III trial comparing imatinib alone with imatinib in combination with interferon or cytarabine, with the primary outcome being molecular remission.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence reviewed, the Hematology DSG drafted the following recommendations:

Target Population

The recommendations apply to adult patients with CML, including those with accelerated and blastic phases of disease.

Draft Recommendations

- Imatinib is recommended as first-line therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia. The initial recommended dose of therapy is 400 mg, given orally, on a daily basis. For patients who do not demonstrate a complete hematologic response after three months of therapy or at least a minor cytogenetic response after 12 months of therapy, the dose of imatinib should be increased to 400 mg, given orally, twice daily.

- Imatinib is recommended for patients who have become refractory to or intolerant of previous therapy (e.g., interferon +/- cytarabine, hydroxyurea) or who have disease progression to accelerated or myeloid blastic phases of the disease. For patients with accelerated or myeloid blastic phases of the disease, the starting dose of imatinib should be 600 mg, given orally, on a daily basis with an increase in dose to 400 mg, given orally, twice daily, if an adequate hematologic or cytogenetic response is not observed.

Qualifying Statements

- The Hematology Disease Site Group considers the current evidence insufficient to make recommendations regarding the duration of imatinib therapy for those in chronic phase, whether or not they are in complete hematologic and major cytogenetic remission. It is unclear whether alternative therapy would improve the outcome of patients who have failed to attain major cytogenetic remissions or who relapse from previous remission. At present, the Hematology Disease Site Group feels that all patients taking imatinib therapy could be maintained on this therapy, with or without additional therapy, until further information becomes available. The role of additional cytogenetic monitoring, other than that performed at 12 months as per the International Randomized Study of Interferon and STI571 trial or to assist in the decision-making process for transplantation, is at present uncertain. Eventually, failure to attain a major cytogenetic remission may become an indication for alternative or combined therapy when such therapies become established.
For patients with chronic phase chronic myeloid leukemia who have had a hematologic and cytogenetic response to interferon (+/- cytarabine) and are tolerating this therapy, treatment decisions are more difficult. Patients should be aware of data demonstrating that, in comparison with interferon (+/- cytarabine), imatinib is associated with superior effectiveness and quality-of-life assessments and less toxicity. In addition, for those who achieve complete cytogenetic responses with either therapy, suppression of BCR-ABL levels is greater in those who are treated with imatinib. These benefits must be weighed against the lack of data describing the long-term effects of this medication and knowledge about potential drug resistance. The Hematology Disease Site Group considers it reasonable for physicians to recommend a change in therapy from interferon (+/- cytarabine) to imatinib, as many patients cannot remain on interferon-containing regimens long term, imatinib is associated with the benefits described above, and survival with imatinib therapy is unlikely to be inferior.

The place of bone marrow transplantation in the initial treatment of chronic myeloid leukemia has not been assessed in randomized trials. Prior imatinib therapy does not appear to compromise the results of transplantation except possibly through delays in its initiation. Patients for whom transplantation will be recommended as a second-line treatment after failure to achieve a major cytogenetic remission with imatinib should have a cytogenetic analysis testing no later than 12 months following the commencement of therapy.

To date, the Hematology Disease Site Group has not reached consensus on the management of patients with chronic myeloid leukemia that has progressed into a lymphoid blastic phase. Preliminary results of testing imatinib in these patients have shown that any responses are usually of very short duration. The potential to use other treatments, such as regimens commonly used to treat acute lymphoblastic leukemia, should be considered.

Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Report #6-3: Drug Therapy for Chronic Myeloid Leukemia.

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 100 practitioners in Ontario (63 hematologists and 37 medical oncologists). 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 November 17, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.

Results
Forty-one responses were received out of the 100 surveys sent (41% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 22 indicated that the report was relevant to their clinical practice, one was unsure if it was relevant, and one left the question unanswered; these 24 practitioners completed the survey. Another practitioner who was unsure if the report was
relevant did not complete the survey. Key results of the practitioner feedback survey are summarized in Table 6.

### Table 6. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>24 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>23 (96%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>22 (92%)</td>
<td>0</td>
<td>2 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>24 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>23 (96%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>21 (88%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>22 (92%)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>18 (75%)</td>
<td>2 (8%)</td>
<td>4 (17%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Summary of Written Comments

Five respondents (21%) provided written comments. The main points contained in the written comments were:

1. One practitioner expressed concern over the minimal discussion of the role that transplantation may have in patients who meet current criteria for imatinib treatment and suggested using historical data because of the lack of RCT data. This respondent also commented that transplantation after imatinib is effective but questioned whether transplantation could be given as first-line treatment in appropriate patients with subsequent administration of imatinib for refractory disease.

2. The same practitioner questioned whether patients being treated with hydroxyurea and remaining in stable phase should be switched to treatment with imatinib.

3. One practitioner expressed the need for a broader treatment guideline for CML.

4. One practitioner commented that new data were available but was uncertain how those should be incorporated.

### Modifications/Actions

1. No changes were made to the recommendations in response to the comment regarding the minimal discussion of the role of transplantation. No randomized trials comparing the results of imatinib therapy with that of transplantation are available. During practitioner feedback, additional follow-up data of the IRIS study became available (37); the estimated overall survival at 24 months for patients randomized to receive imatinib therapy was 96%. Those results are superior to published studies evaluating transplantation (38,39). The first 24
months after transplantation is the period of highest risk for mortality, and any postulation regarding a superior survival with transplantation could only be shown with comparisons of those treatments beyond that time. No data are available to make such a long-term comparison possible, and only randomized trials directly comparing imatinib with transplantation or investigating the use of imatinib in conjunction with transplantation can provide answers.

2. No changes were made to the recommendations in response to the inquiry about patients in stable condition on therapy with hydroxyurea. The survival of patients treated with hydroxyurea is concluded to be inferior to those receiving imatinib, based on strong, though indirect, evidence. A meta-analysis of randomized trials reveals that hydroxyurea is inferior to interferon (6), and interferon was shown to be inferior to the interferon plus cytarabine combination (7). No difference in survival at 18 months was detected between interferon plus cytarabine and imatinib (15), but imatinib is unlikely to be inferior long term. In general, therefore, all patients on hydroxyurea, even when in hematological remission, should have their treatment changed to imatinib.

3. In response to the plea for a broader guideline for CML, the DSG agrees with the need for information on a number of questions, particularly with respect to the place of transplantation and the optimal treatment for those failing to achieve cytogenetic or molecular remissions with imatinib. The recommendations presented in this guideline are based on published evidence, and the lack of direction on some specific clinical situations reflects the lack of such evidence. The DSG will explore evaluating these topics in future updates of this guideline.

4. The Hematology DSG will incorporate any new data at the next update. The Hematology DSG tries to keep guideline reports as up-to-date as possible, especially when aware of new and important trials that are newly published.

**Practice Guidelines Coordinating Committee Approval Process**

The practice guideline report was circulated to members of the PGCC for review and approval. Eight of 14 members returned ballots, of which one member was also a member of the Hematology DSG and did not review the report. Six PGCC members approved the guideline report as written, and one member approved the guideline and suggested replacing the phrase "on a daily basis" with "once daily" in the two recommendation bullets. In addition, one PGCC member recommended forwarding the approved guideline to the Policy Advisory Committee and to the Systemic Therapy leaders for policy consideration.

*Modifications/Actions*

The Hematology DSG incorporated the suggested change to the recommendation bullets. The approved guideline report will be forwarded as "for information" to the Policy Advisory Committee and Systemic Therapy leaders.

**VIII. POLICY IMPLICATIONS**

This report was submitted as a draft evidence summary to the Policy Advisory Committee (PAC) in October 2001, who then forwarded the draft to the Drug Quality and Therapeutics Committee (DQTC) for review. In January 2002, the DQTC recommended that imatinib not be listed in the Drug Formulary but be considered for expedited reimbursement through the Individual Clinical Review (Section 8) mechanism for:

- Treatment of CML in blast crisis: doses up to 600 mg per day will be approved.
- Treatment of CML in accelerated phase: doses up to 400 mg per day will be approved.
All other requests for imatinib: will undergo external Individual Clinical Review.

This report was submitted as a draft practice guideline to the PAC in September 2003, who then forwarded recommendations to the Ontario Drug Board (ODB). Recommendations in the draft practice guideline submitted to the PAC were:

- Imatinib is recommended as first-line therapy in newly diagnosed patients with Philadelphia chromosome-positive CML. The initial recommended dose of therapy is 400 mg, given orally, on a daily basis.
- For patients who do not demonstrate a complete hematologic response after three months of therapy or at least a minor cytogenetic response after 12 months of therapy, the dose of imatinib should be increased to 400 mg, given orally, twice daily.
- Imatinib is recommended for patients who have become refractory to or intolerant of previous therapy (e.g., interferon +/- cytarabine, hydroxyurea) or who have disease progression to accelerated or myeloid blastic phases of disease.
- For patients with accelerated or myeloid blastic phases of disease, the starting dose of imatinib should be 600 mg, given orally, on a daily basis with an increase in dose to 400 mg, given orally, twice daily, if an adequate hematologic or cytogenetic response is not observed.

The PAC agreed with the recommendations and concluded that the draft practice guideline should be forwarded to the ODB with a recommendation regarding the appropriate frequency of molecular testing for monitoring purposes.

IX. PRACTICE GUIDELINE
This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and by the Practice Guidelines Coordinating Committee.

Target Population
These recommendations apply to adult patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease.

Recommendations
- Imatinib is recommended as first-line therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia. The initial recommended dose of therapy is 400 mg, given orally, once daily. For patients who do not demonstrate a complete hematologic response after three months of therapy or at least a minor cytogenetic response after 12 months of therapy, the dose of imatinib should be increased to 400 mg, given orally, twice daily.

- Imatinib is recommended for patients who have become refractory to or intolerant of previous therapy (e.g., interferon +/- cytarabine, hydroxyurea) or who have disease progression to accelerated or myeloid blastic phases of the disease. For patients with accelerated or myeloid blastic phases of the disease, the starting dose of imatinib should be 600 mg, given orally, once daily with an increase in dose to 400 mg, given orally, twice daily, if an adequate hematologic or cytogenetic response is not observed.

Qualifying Statements
- The Hematology Disease Site Group considers the current evidence insufficient to make recommendations regarding the duration of imatinib therapy for those in chronic phase, whether or not they are in complete hematologic and major cytogenetic remission. It is unclear whether alternative therapy would improve the outcome of patients who have failed
to attain major cytogenetic remissions or who relapse from previous remission. At present, the Hematology Disease Site Group feels that all patients taking imatinib therapy could be maintained on this therapy, with or without additional therapy, until further information becomes available. The role of additional cytogenetic monitoring, other than that performed at 12 months as per the International Randomized Study of Interferon and STI571 trial or to assist in the decision-making process for transplantation, is at present uncertain. Eventually, failure to attain a major cytogenetic remission may become an indication for alternative or combined therapy when such therapies become established.

- For patients with chronic phase chronic myeloid leukemia who have had a hematologic and cytogenetic response to interferon (+/- cytarabine) and are tolerating this therapy, treatment decisions are more difficult. Patients should be aware of data demonstrating that, in comparison with interferon (+/- cytarabine), imatinib is associated with superior effectiveness and quality-of-life assessments and less toxicity. These benefits must be weighed against the lack of data describing the long-term effects of this medication and knowledge about potential drug resistance. The Hematology Disease Site Group considers it reasonable for physicians to recommend a change in therapy from interferon (+/- cytarabine) to imatinib, as many patients cannot remain on interferon-containing regimens long term, imatinib is associated with the benefits described above, and survival with imatinib therapy is unlikely to be inferior.

- The clinical importance of observed molecular responses in newly diagnosed patients with chronic phase chronic myeloid leukemia who achieved complete cytogenetic responses with imatinib therapy is evolving and was not addressed at this time.

- The place of bone marrow transplantation in the initial treatment of chronic myeloid leukemia has not been assessed in randomized trials. Prior imatinib therapy does not appear to compromise the results of transplantation except possibly through delays in its initiation. Patients for whom transplantation will be recommended as a second-line treatment after failure to achieve a major cytogenetic remission with imatinib should have a cytogenetic analysis testing no later than 12 months following the commencement of therapy.

- To date, the Hematology Disease Site Group has not reached consensus on the management of patients with chronic myeloid leukemia that has progressed into a lymphoid blastic phase. Preliminary results of testing imatinib in these patients have shown that any responses are usually of very short duration. The potential to use other treatments, such as regimens commonly used to treat acute lymphoblastic leukemia, should be considered.

Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Report #6-3: Drug Therapy for Chronic Myeloid Leukemia.

XI. ACKNOWLEDGEMENTS
The Hematology Disease Site Group would like to thank Drs Irwin Walker and Ralph Meyer and Ms. Julie Makarski and Ms. Adrienne Stevens for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Hematology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at http://www.cancercare.on.ca/.
REFERENCES


Appendix I. Literature search strategy used for searching MEDLINE and CANCERLIT.\textsuperscript{a}

1  exp Leukemia, Myeloid, Chronic/
2  Leukemia, Myeloid/
3  exp Leukemia, Myeloid, Philadelphia-Positive/
4  leuk?emia.mp.\textsuperscript{b}
5  1 or 2 or 3 or 4
6  STI571.mp.
7  STI 571.mp.
8  imatinib.mp.\textsuperscript{c}
9  6 or 7 or 8
10 CGP57148B.mp.
11 CGP 57148.mp.
12 cgp 57148B.mp.
13 10 or 11 or 12
14 CGP 57148.rn.
15 13 or 14
16 Glivec.mp.
17 Gleevec.mp.
18 16 or 17
19 9 or 15 or 18
20 5 and 19
21 limit 20 to human
22 limit 21 to english language

\textsuperscript{a}CANCERLIT is longer being searched as of July 2003.
\textsuperscript{b}Modified from “leukemia” to “leuk?emia” in the April 2003 literature search.
\textsuperscript{c}Added in the April 2003 literature search.

A modified strategy of the above was used for PREMEDLINE. Because of the change in inclusion criteria for this report, the following publication-type search strategy was combined with the above in the July 2003 literature search:

23  exp practice guidelines/
24  exp guidelines/
25  guideline?.tw,pt,sh.
26  (practice guideline or guideline?).mp,pt.
27  consensus.sh,tw,pt.
28  or/23-27
29  controlled:.sh,tw,pt.
30  clinical trial?.sh,tw,pt.
31  (double-blind: or single-blind:).sh,tw.
32  multicent: stud:.mp.
33  multicenter study.pt.
34  placebos/
35  comparative study/
36  or/29-35
37  exp randomized controlled trials/
38  random::mp,pt.
39  37 or 38
40  meta-analysis.mp,pt.
(meta-anal: or metaanal: or metanal:).tw.
(systematic: review? or systematic: overview?).tw.
(quantitativ: review? or quantitativ: overview?).tw.
(methodologic: review? or methodologic: overview?).tw.
quantitativ: synthes:.tw.
or/40-45
letter.pt.
comment.pt.
editorial.pt.
or/47-49
28 or 36 or 39 or 46
22 and 51
52 not 50
Evidence-Based Series #6-15: Section 4- ARCHIVED 2013

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

Interferon-alfa in the Treatment of Patients
with Inoperable Locally Advanced or Metastatic Renal Cell Cancer

Guideline Summary Review

Cheung M, Ako Arrey D, and Members of the Hematology Cancer Disease Site Group

The 2004 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be
maintained by may still be useful for academic or other
information purposes

Review Date: August, 2013

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2004.

In November 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (MC) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be archived. The Hematology Disease Site Group (DSG) archived the recommendations found in Section 1 (Clinical Practice Guideline) in November 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. What is the role of imatinib (STI571, GleevecTM, Glivec®) in treating patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease? Outcomes of interest, in decreasing order of importance, include survival, quality of life, duration of treatment response, toxicity, hematologic response, and cytogenetic or molecular response.

Literature Search and New Evidence
The new search (July 2003 to July 2013) yielded no new full text publications or abstracts of RCTs that compared adjuvant radiation therapy after surgery to surgery alone. An additional search for ongoing studies on Clinicaltrials.gov yielded 1 potentially relevant ongoing RCT. Brief results of these searches are shown in the Document Review Tool.

**Impact on Guidelines and Its Recommendations**  
The new data contradicts existing recommendations. Therefore, the Hematology DSG ARCHIVED the 2004 recommendations on postoperative adjuvant radiation therapy in stage II or IIIA completely resected non-small cell lung cancer.
What is the role of imatinib (STI571, GleevecTM, Glivec®) in treating patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease? Outcomes of interest, in decreasing order of importance, include survival, quality of life, duration of treatment response, toxicity, hematologic response, and cytogenetic or molecular response.

Target Population

These recommendations apply to adult patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease.

Inclusion Criteria

For literature searches conducted from July 2003 to July 2013, articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with CML of any phase.

2. Phase I or II trials reporting the safety and efficacy of imatinib in patients with CML of any phase. For literature searches conducted from July 2003 onward, articles were selected for inclusion if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with CML of any phase.

2. Systematic reviews or practice guidelines assessing imatinib in patients with CML of any phase.

Exclusion Criteria

For literature searches conducted from July 2003 to July 2013, reports excluded from consideration included:

1. Pilot studies describing use of imatinib in combination with other drugs.

2. Studies investigating the role of imatinib post-transplantation. For literature searches conducted from November 2002 onward, reports excluded from consideration included:

3. Studies investigating the role of imatinib post-transplantation
**Search Details:**
- Embase 1996 to 2013 week 28
- Ovid MEDLINE (R) 1946 to July Week 2 2013
- Ovid MEDLINE (R) Daily updates July 10 2013
- www.cancer.gov/clinicaltrials

**Results**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N of studies</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (n=187) versus IFN-alpha regimens (n=650)</td>
<td>Patients with newly diagnosed Ph-positive CML in chronic phase</td>
<td>1982 until 1997</td>
<td>CCyR Survival</td>
<td>The complete cytogenetic response (Ph 0%) rates were better with imatinib (81% vs. 32%; P &lt; 0.001) Survival rates (30-month estimated survival rates 98% vs. 88%; P = 0.01). A multivariate analysis of the total study group of 837 patients identified imatinib therapy to be a significant independent favorable prognostic factor for survival (P = 0.01).</td>
<td>Kantarijan HM et al, 2003</td>
</tr>
<tr>
<td>Imatinib mesylate at a dose of 400 mg/day.</td>
<td>Japanese patients in the first chronic phase of CML (n=39)</td>
<td>n/a</td>
<td>CHR CCRPCR</td>
<td>Hematologic complete response was obtained in 92.3% of the patients. Complete cytogenetic response (CR) was obtained in 43.6%, and major partial CR was obtained in 20.5% of the patients. Although 29 of 39 patients required an adjustment of dosing because of grade 3 or 4 adverse events, most of the events were reversible, and 25 of the 29 patients were able to resume therapy. Between day 15 and day 35, grade 3 or 4 neutropenia and/or leukocytopenia occurred in 13 patients, and grade 3 thrombocytopenia occurred in 5 patients. Overall, nonhematologic grade 3 adverse events occurred in 28.2% of the patients.</td>
<td>Yasuo Morishima et al, 2004</td>
</tr>
<tr>
<td>To evaluate the effectiveness of imatinib as first-line treatment for chronic myeloid</td>
<td>Patients with chronic myeloid leukemia</td>
<td>12 months</td>
<td>Survival HR CR</td>
<td>Imatinib was associated with complete CR at 12 months follow-up of 68% compared with 20% for the IFN-α plus Ara-C group. The estimated proportion of people</td>
<td>K Dalziel et al, 2004</td>
</tr>
</tbody>
</table>
leukaemia (CML) compared with interferon-alpha (IFN-α), hydroxyurea and bone marrow transplantation (BMT) taking imatinib who had not progressed to accelerated or blast phases at 12 months was 98.5%, and 93.1% for IFN-α plus Ara-C

Overall survival was not statistically significantly different.

Withdrawal due to side-effects was 2% for imatinib and 5.6% for IFN-α plus Ara-C. Cross-over due to intolerance was 0.7% and 22.8% for imatinib and for IFN-α plus Ara-C, respectively.

Quality of life was better in the imatinib group than the IFN-α group when assessed at 1, 3 and 6 months.

The incremental cost-effectiveness ratio (ICER) of imatinib compared with IFN-α from the independent model was £26,180 per quality-adjusted-life-years (QALY) gained and was relatively robust; imatinib was less cost-effective than hydroxyurea with an ICER of £86,934

Imatinib appears to be more effective than current standard drug treatments in terms of cytogenetic response and progression-free survival, with fewer side-effects. However, there is uncertainty concerning longer term outcomes, the development of resistance to imatinib, the duration of response and the place of imatinib relative to BMT. New issues are continually arising, such as optimal management pathways and combination therapies.

<table>
<thead>
<tr>
<th>Imatinib</th>
<th>Patients with chronic myeloid leukemia (CML)</th>
<th>Articles published between 1996 and 2006</th>
<th>n/a</th>
<th>The estimated 3-year survival rate for patients treated with imatinib in the IRIS trial was 92% compared with 84% for patients treated with IFN-plus cytarabine in the CML91 study</th>
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<tbody>
<tr>
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<td>The estimated 3-year survival rate for patients treated with imatinib in the IRIS trial was 92% compared with 84% for patients treated with IFN-plus cytarabine in the CML91 study</td>
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<td>Recommended CML Monitoring Schedule: Hematologic (At baseline and every 2–4 wk until CHR, then every 1–3 mo); Cytogenetic (At Elias Jabbour et al., 2007</td>
</tr>
</tbody>
</table>
baseline and every 3–6 mo until confirmed CCyR; then every 12–18 mo); Molecular (Every 3 mo in CCyR until MMR; then every 3–6 mo thereafter; more frequently if rising RQ-PCR values)

| Imatinib | Patients with chronic myeloid leukaemia who received imatinib. | Medical literature from 1980 to 2007 | n/a | Imatinib is effective and generally well tolerated in patients with Ph+ CML. In patients with newly diagnosed chronic-phase CML, imatinib was more effective than interferon-α plus cytarabine in preventing progression of the disease and in achieving haematological and cytogenetic responses. Overall survival rates remain high after 5 years of follow-up, and historical comparisons with other treatments demonstrate improved overall survival with imatinib in the long term. Patients with accelerated-phase or blast-crisis CML, or those who have not responded to prior interferon-α therapy also benefit from imatinib treatment. Some patients become resistant or intolerant to imatinib therapy; management strategies to overcome these problems include dosage adjustment, other treatments, or combination therapy with imatinib and other agents. | Marit D. Moen et al, 2007 |

**Imatinib**

**mesylate given orally at a daily dose of 400 mg versus**

Dose escalation to either 600 mg or 800 mg daily.

<p>| Patients with chronic myeloid leukemia (CML) in chronic phase (CML-CP) n=106 | 3 years | Survival &amp; Response | Among all 106 patients who underwent dose escalation, the rates of freedom from progression to accelerated phase or blast phase and overall survival were 89% and 84% at 3 years after dose increase, respectively. A cytogenetic response was obtained in 42% of patients who had their dose escalated based on protocol criteria and in 38% of patients who had their dose escalated according to the European LeukemiaNet recommendations. The results from this retrospective analysis supported imatinib dose escalation as an appropriate initial option for patients with CML-CP who | Hagop M. Kantarjian et al, 2009 |</p>
<table>
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<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Trials</th>
<th>Response</th>
<th>Outcome</th>
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<tr>
<td>Imatinib 400 mg daily</td>
<td>Patients with chronic phase chronic myeloid leukemia (CP-CML)</td>
<td>Four</td>
<td>CCyR</td>
<td>At 12 months, high dose compared with standard dose imatinib improved complete cytogenetic response (CCyR) (RR 1.17, 95% CI 1.08-1.26, four trials, I(2) = 33%) as well as major molecular response (MMolR) (RR 1.26, 95% CI 1.12-1.42, four trials, I(2) = 0%). There was no difference in all-cause mortality or disease progression at the end of follow up. Adverse events requiring discontinuation were more common in the high-dose arm (RR 1.98, 95% CI 1.20-3.26, three trials, I(2) = 0%), as were Grade III/IV neutropenia and thrombocytopenia: RR 1.56, 95% CI 1.15-2.12 and RR 1.86, 95% CI 1.28-2.70, respectively. There is currently insufficient evidence to support the routine use of higher doses of imatinib as frontline treatment for CP-CML.</td>
<td>Gafter-Gvili A et al, 2011</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Chronic myelogenous leukemia patients in US and Japan.</td>
<td></td>
<td></td>
<td>Estimated age-standardized mortality rates decreased significantly in both countries after the availability of imatinib. The annual percent changes (95% confidence interval) in the U.S. were 12.3% (14.8% to 9.7%) for men and 11.6% (13.1% to 10.1%) for women. In Japan, these were 20.8% (36.2% to 1.6%) for men and 15.6% (18.8% to 12.2%) for women. The period of change in the mortality trend seems to correlate with the period in which imatinib appeared in the two countries. The CML mortality rate in 2008 was nearly 30% that of the 1993 level.</td>
<td>Dai Chihara et al, 2012</td>
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<tr>
<td>Imatinib</td>
<td>Adult patients with chronic</td>
<td>n/a</td>
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<td>By 18 months, 47% of patients had received cytogenetic response assessment continuously as</td>
<td>Lei Chen et al, 2012</td>
</tr>
</tbody>
</table>

**Notes:**
- CCyR: Complete Cytogenetic Response
- MMR: Major Molecular Response
- AEs: Adverse Events
- RR: Risk Ratio
- CI: Confidence Interval
- I(2): Heterogeneity Index
<table>
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<tr>
<th>Study</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Result</th>
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<tr>
<td>Dasatinib 100 mg daily versus Nilotinib 600/800 mg daily versus Imatinib 400 mg daily</td>
<td>Newly diagnosed chronic myeloid leukemia</td>
<td>Eight clinical studies (3,520 individuals)</td>
<td>CCyR MMR</td>
</tr>
<tr>
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<td>At six months, the odds of complete cytogenetic response (CCyR) for dasatinib and nilotinib were approximately three times those for imatinib (range 2.77 to 3.06, all values not significant). At twelve months dasatinib and nilotinib were significantly better than imatinib for both CCyR and major molecular response (MMR) (CCyR odds range 2.06 to 2.41, MMR odds range 2.09 to 2.87). At eighteen months dasatinib and nilotinib were again significantly better in terms of CCyR than imatinib (response odds 1.55 to 2.01). When dasatinib and nilotinib were compared to each other, for both clinical endpoints at all time points the response odds were not significantly different. On the basis of a systematic review of the current literature base, dasatinib 100 mg, nilotinib 600 mg and nilotinib 800 mg should be viewed as equivalent in terms of complete cytogenetic and major molecular response.</td>
</tr>
<tr>
<td>Imatinib versus Interferon plus cytarabine combination</td>
<td>Patients with CP chronic myeloid leukaemia up to 5 years</td>
<td>Survival Adverse Events</td>
<td>Survival rate was 89% with imatinib, versus about 70% in previous clinical trials of interferon plus cytarabine. Fewer than 2% of patients relapsed after responding to imatinib. At 5 years the overall survival rate was 79%, versus about 50% with standard treatments. As second-line treatment for patients in the accelerated phase, they presented follow-up data on 235 patients. After 3 years 55% of the</td>
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</table>
patients were still alive, while the usual survival time is 3 to 18 months.

As second-line treatment of the blast crisis, they presented non-comparative follow-up data on 260 patients. After 3 years 14% of the patients were still alive, while the usual survival time for patients at this stage is 2 to 4 months.

A new study was a non-comparative follow-up study of 50 children and adolescents aged 2 to 19 years treated with imatinib. The estimated 2-year survival rate was 84%. The haematological and cytogenetic response rates were similar to those reported in adults.

The initial clinical evaluation of imatinib showed that its main adverse effects were nausea and vomiting, oedema, fluid retention, muscle cramps, and cutaneous disorders. It was estimated that heart failure occurred in 1 to 10 per 1000 patients. A study of 54 patients confirmed the high incidence of cutaneous disorders. Cases of prostate and bladder cancer have been reported in patients treated with imatinib in France. A study of 16 patients suggests that imatinib might alter bone metabolism. In France, treatment with imatinib costs about 25% more than the interferon plus cytarabine combination.

In practice, imatinib seems to increase survival time when used as a first-line or second-line treatment for patients in different phases of chronic myeloid leukaemia.

<table>
<thead>
<tr>
<th>Imatinib mesylate (IM)</th>
<th>Patients with chronic myeloid leukemia (CML) n=177</th>
<th>Median of 60 months (range, 24-116 months)</th>
<th>HR CR MR EFS OS AEs</th>
<th>Complete hematologic response (CHR) was achieved in 90% of patients at 3 months (median time, 2.02 months)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Complete cytogenetic response (CCyR) was achieved in a significantly higher proportion of patients within the low and intermediate Sokal risk group (79.4%, 85.2%) compared with the high risk patients (14.3%, p=0.001).</td>
</tr>
</tbody>
</table>

No author (conference abstract)
There was a significant difference in the complete molecular response (CMR) ratio achieved by low, intermediate and high Sokal risk patients (70.4%, 63.8% and 33.3%, p<0.05).

5-year OS rates were 100% and 84% among low-intermediate and high Sokal risk patients (p=0.0001).

The EFS at 5 years was 77%, 81%, and 63% in low, intermediate and high Sokal risk patients (p=0.001).

Early Chronic Phase (ECP) CML patients achieved higher CCyR rates (87%) compared with Late Chronic Phase (LCP) CML patients (46.6%, p=0.001).

CMR rates were 67.7% and 46.9% in ECP and LCP CML patients (p<0.05). 62.2% of the patients remained on 400 mg/day IM treatment and in 3.4% the dose was increased to 600 mg/day.

Hematological and non-hematological toxicities were experienced in 23.7% and 56.7% of the patients.

5-year OS and EFS rates of the entire cohort were calculated as 97% and 77%.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
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<tbody>
<tr>
<td>Imatinib 400 mg daily versus Interferon alpha (IFN up to 5 MU/m2/d with cytarabine (Ara-C) 20 mg/m2/d added for 10 days every month (IFN + LDAC</td>
<td>Newly diagnosed patients with chronic-phase chronic myeloid leukemia (CML) (n=1106)</td>
<td>6.9.12 and 18</td>
<td>Quality of Life (using the Trial Outcome Index -TOI - a composite endpoint of physical/functional/treatment subscales)</td>
<td>Two hundred sixty-one patients (50%) crossed over from IFN to imatinib and 11 (2%) crossed over from imatinib to IFN. There was a significant decline in TOI scores for the IFN treatment arm compared with preservation of baseline TOI scores in the imatinib arm (P &lt; .001, ITT). Mean social/family and Emotional and Well Being scores were 22.8 and 19.5, respectively, for imatinib and 21.6 and 17.6, respectively, for IFN. After crossing over from IFN to imatinib, patients experienced a significant (P &lt; .001) increase in TOI scores.</td>
<td>Elizabeth H Hahn et al, 2003</td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Outcome 1</td>
<td>Outcome 2</td>
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<tr>
<td>Imatinib versus Interferon alfa</td>
<td>Chronic-myeloid leukaemia</td>
<td>n/a</td>
<td>CCyR</td>
<td>Patients on imatinib showed an overall survival advantage (relative risk 0.54, 95% CI 0.31-0.93).</td>
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<td>However, although patients on imatinib who achieved at least some degree of cytogenetic response after 6 months had better survival than controls (0.13, 0.05-0.39), those with no cytogenetic response to imatinib had significantly worse survival (1.69, 1.09-2.64).</td>
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<td>Findings suggest that cytogenetic responders obtain benefit from imatinib but patients who show no cytogenetic response should be given alternative treatment without delay</td>
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<tr>
<td>Imatinib Versus Interferon alfa</td>
<td>Patients with chronic-myeloid leukemia (CML)</td>
<td>12 months</td>
<td>CCR</td>
<td>In the Imatinib group, levels of BCR-ABL transcripts after 12 months of treatment had fallen by at least 3 log in 57 percent and 24 percent of those in the group given interferon plus</td>
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</tbody>
</table>

Imatinib offers clear QoL advantages over IFN as first-line treatment of chronic-phase CML. In addition, patients who crossed over to imatinib reported higher QoL than those who remained on IFN.

The projected probability of achieving a complete cytogenetic response was 76.2% for imatinib and 14.5% for IFN/LDAC.

Freedom from progression to accelerated phase or blast crisis was 96.7% for imatinib versus 91.5% for IFN/LDAC.

At the time of the analysis, 85.7% of imatinib-treated patients continued on first-line therapy, but only 10.8% of patients continued with IFN/LDAC.

Most cross-overs to imatinib were due to interferon-intolerance.

Overall survival was not different in the two groups at 19 months, reflecting efficient rescue of IFN/LDAC failures with imatinib.

Imatinib should now be considered the standard therapy for newly diagnosed patients with CML.
<table>
<thead>
<tr>
<th>plus cytarabine</th>
<th>chronic phase (n=1106)</th>
<th>cytarabine (P = 0.003). On the basis of the rates of complete cytogenetic remission of 68 percent in the imatinib group and 7 percent in the group given interferon plus cytarabine at 12 months, an estimated 39 percent of all patients treated with imatinib but only 2 percent of all those given interferon plus cytarabine had a reduction in BCR-ABL transcript levels of at least 3 log (P&lt;0.001)</th>
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<tbody>
<tr>
<td><strong>Imatinib</strong></td>
<td><strong>Newly diagnosed chronic-phase chronic myeloid leukemia (CML) patients (n=55)</strong></td>
<td><strong>24 months</strong> Hematologic and cytogenic responses First-line imatinib-treated patients had profound reductions in BCR-ABL/BCR%, which significantly exceeded those of IFN+AraC-treated patients BCR-ABL/BCR% levels were measured by real-time quantitative RT-PCR and were significantly lower for the imatinib-treated patients at all time points up to 18 months, P&lt;0.0001</td>
</tr>
<tr>
<td>versus <strong>Interferon-alfa plus cytarabine (IFN+AraC)</strong></td>
<td></td>
<td>Branford S et al, 2003</td>
</tr>
<tr>
<td><strong>Imatinib (n=553)</strong></td>
<td><strong>Patients with Chronic Myeloid Leukemia</strong></td>
<td><strong>5 years</strong> EFS hematologic, cytogenetic, and molecular responses and adverse events. Complete cytogenetic response among patients receiving imatinib were 69% by 12 months and 87% by 60 months. An estimated 7% of patients progressed to accelerated-phase CML or blast crisis, and the estimated overall survival of patients who received imatinib as initial therapy was 89% at 60 months. At 60 months, the estimated rate of event-free survival was 83% (95% confidence interval [CI], 79 to 87), and an estimated 93% of patients (95% CI, 90 to 96) had not progressed to the accelerated phase or blast crisis Of the 553 patients receiving imatinib, 35 (6%) progressed to the accelerated phase or blast crisis, 14 (3%) had a hematologic relapse, 28 (5%) had a loss of major cytogenetic response, and 9 (2%) died from a cause unrelated to CML. The most commonly reported adverse events were edema (including peripheral and periorbital edema) (60%), muscle cramps (49%), diarrhea (45%), nausea (50%), musculoskeletal pain (47%), rash and other skin problems (40%), abdominal</td>
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<td>versus <strong>Interferon alfa plus cytarabine (n=553)</strong></td>
<td></td>
<td>Brian Druker et al, 2006</td>
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<tr>
<td>Treatment</td>
<td>Patient Description</td>
<td>Duration</td>
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<tr>
<td>Imatinib (n= 551) Versus interferon plus cytarabine (IFN/Ara-C) (n=325)</td>
<td>Patients with newly diagnosed chronic-phase chronic myelogenous leukemia (CP CML)</td>
<td>42 months</td>
</tr>
<tr>
<td>Imatinib mesylate (n=279) versus Interferon-alpha-based regimens (n=650)</td>
<td>Newly diagnosed Philadelphia chromosome (Ph)-positive chronic-phase chronic myelogenous leukemia (CML)</td>
<td>3 years</td>
</tr>
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</table>
### Imatinib (n=553) Versus Interferon-α (IFN) plus cytarabine (n=553)

<table>
<thead>
<tr>
<th>400mg/d (SD-IM) versus 800mg/d (HD-IM) of imatinib mesylate (IM)</th>
<th>patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase (CML-CP)</th>
<th>24 Months</th>
<th>CCyR MMR</th>
<th>EFS</th>
<th>PFS</th>
<th>OS</th>
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<tr>
<td>Imatinib (n=553)</td>
<td>Adult patients (aged 18–70 years) with previously untreated Ph+ Chronic Myeloid Leukemia - Chronic</td>
<td>6 years</td>
<td>6 years</td>
<td>EFS</td>
<td>6 years</td>
<td>6 years</td>
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<tr>
<td>Versus Interferon-a (IFN) plus cytarabine (n=553)</td>
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There was no significant difference in the cumulative rates of CCyR at 24 mos (76% in each arm).

Overall, 9 (6%) pts on SD-IM and 15 (5%) pts on HD-IM had experienced an event (loss of complete hematologic response, loss of major cytogenetic response, progression to accelerated phase and blast crisis, or death due to any cause).

There were no significant differences in estimated EFS (SD-IM: 95% vs. HD-IM: 95%), PFS (97% vs. 98%), or OS (97% vs. 98%) at 24 mos.

Patients in both arms combined who had <=1 dose interruption during the first 12 mos achieved higher MMR rates at 12 (57.1% vs 33.3% for <=1 vs > 1 interruption; P < 0.0001) and 18 mos (72.6 vs. 46.8; P < 0.0001), faster time to MMR (P = 0.0002), and higher CCyR rates at 12 mos (88.8 vs 63.8; P < 0.0001), compared with pts who had > 1 dose interruption during the same period. On the SD-IM arm pts with <=1 (vs > 1) dose interruption also had higher MMR rates at 12 and 18 mos (12 mos: 49.6% vs 22.2%, P = 0.04; 18 mos: 70.9% vs 50%, P = NS). Comparing pts in the HD-IM arm with DI >=600mg/d for the first 12 mos vs DI < 600 mg/d, the MMR rates at 12 mos (62.4% vs 34.1%, P < 0.0001) and 18 mos (75.2% vs 40.3%, P < 0.0001) were higher, the time to MMR was faster (P < 0.0001), duration of MMR was longer (P = 0.0141) and CCyR rates at 12 mos (89.6% vs 70.3%, P < 0.0001) were higher for pts with DI >=600mg/d.

Hochhaus et al, 2009

Michele Baccarani et al, 2009
<table>
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<tr>
<th>Phase (CML-CP) diagnosed within 6 months of study entry (n=1106)</th>
<th>randomized to receive imatinib and still on study treatment showed CCyR at last assessment. The estimated event-free survival at 6 years was 83%, and the estimated rate of freedom from progression to AP and BC was 93%. The estimated overall survival was 88%—or 95% when only CML-related deaths were considered.</th>
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<tr>
<td>Dasatinib 100 mg (n = 259) versus Imatinib 400 mg (n = 260) once daily</td>
<td>Patients with newly diagnosed chronic-phase (CP) CML (n= 519) 12 Months (CCyR) Complete cytogenetic response was higher with dasatinib than with imatinib (77% vs. 66%, P=0.007) Complete cytogenetic response observed on at least one assessment (83% vs. 72%, P=0.001). The rate of major molecular response was higher with dasatinib than with imatinib (46% vs. 28%, P&lt;0.0001), and responses were achieved in a shorter time with dasatinib (P&lt;0.0001). Progression to the accelerated or blastic phase of CML occurred in 5 patients who were receiving dasatinib (1.9%) and in 9 patients who were receiving imatinib (3.5%).</td>
</tr>
<tr>
<td>Imatinib 400 mg/day versus Imatinib dose or 400 mg plus interferon-alfa.</td>
<td>Adult patients (n=210) with chronic myeloid leukemia less than three months from diagnosis (Sokal high risk: 16%) Median, 50.5 months (1.2 to 78 months) CCR CHR MMR Survival At six months 73.8% of patients were in complete cytogenetic response; among the remainder, 9 could not be randomized (toxicity or consent withdrawal), 17 were assigned to high imatinib dose, and 15 to 400 mg + interferon-alpha. Cumulative response at three years was: complete hematologic response 98.6%, complete cytogenetic response 90% and major molecular response 82%. On an intention-to-treat basis, complete cytogenetic response was 78.8% at 18 months. At five years, survival was 97.5%, survival free from accelerated/blastic phase 94.3%, failure free survival 82.5%, and event free survival (including permanent imatinib discontinuation) 71.5%.</td>
</tr>
<tr>
<td>Imatinib 400 mg</td>
<td>Patients with 12 months Molecular and cytogenetic The rates of cytogenetic response were similar among the four groups.</td>
</tr>
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</table>

**Preudhomme C.**

**Francisco Cervantes et al, 2010**

**Hagop M. Kantarjian et al, 2010**
| Daily versus daily Imatinib (400 mg daily) plus cytarabine (20 mg per square meter of body-surface area per day on days 15 through 28 of each 28-day cycle) versus Pegylated interferon (peginterferon) alfa-2a (90 μg weekly) versus Imatinib alone at a dose of 600 mg daily | Newly diagnosed chronic myeloid leukemia (CML) in the chronic phase (n=636) responses, time to treatment failure, overall and event-free survival, and adverse events | The rate of a superior molecular response was significantly higher among patients receiving imatinib and peginterferon alfa-2a (30%) than among patients receiving 400 mg of imatinib alone (14%) (P=0.001). The rate was significantly higher among patients treated for more than 12 months than among those treated for 12 months or less. Gastrointestinal events were more frequent among patients receiving cytarabine, whereas rash and depression were more frequent among patients receiving peginterferon alfa-2a. |

| Bosutinib 500 mg versus 400 mg Imatinib | Patients with Philadelphia chromosome-positive (Ph+) chronic phase (CP) chronic myeloid leukemia (CML) in the second- and third-line treatment settings (n=502) | CCyR, CHR, MMR, PFS, Adverse events At Week 48 (approximately 11 months), 71.5% and 74.8% of patients (both treatment arms combined) were in CCyR and complete hematologic response (CHR), respectively. During the study, 81.4% of patients achieved a CCyR at or before Week 48, with a median time to CCyR of 24 weeks; 82.6% of patients achieved a CHR, with a median time to CHR of 8 weeks; and 40.6% of patients achieved a major molecular response (MMR), with a median time to MMR of 49 to 61 weeks for the 2 treatment arms. For the combined treatment arms, common treatment-emergent adverse events included diarrhea (43.7%), nausea (32.3%), vomiting (22.0%), rash (16.8%), pyrexia (11.6%), and fatigue (11.0%). The only grade 3 treatment-emergent adverse event observed in 2% of patients was diarrhea (5.2%), which was usually limited to the first weeks of treatment. Grade 3 hematologic laboratory | Carlo Gambacorti-Passerini et al, 2010 |
### Table: Efficacy of Nilotinib 300 mg bid vs Imatinib 400 mg Once Daily in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)</th>
<th>18 months</th>
<th>MMR</th>
<th>OS</th>
<th>PFS</th>
<th>EFS</th>
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<tbody>
<tr>
<td>Nilotinib 300 mg bid (n = 282)</td>
<td></td>
<td>18 months</td>
<td>MMR</td>
<td>OS</td>
<td>PFS</td>
<td>EFS</td>
</tr>
<tr>
<td>versus Nilotinib 400 mg bid (n = 281)</td>
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<tr>
<td>versus Imatinib 400 mg once daily (n = 283)</td>
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</table>

Abnormalities included neutropenia (14.2%), thrombocytopenia (12.4%), and anemia (5.8%).

The overall best MMR rate was superior for nilotinib 300 mg bid (66%, \( P < .0001 \)) and nilotinib 400 mg bid (62%, \( P < .0001 \)) compared with imatinib (40%).

Superior rates of MMR were observed in both nilotinib arms compared with the imatinib arm across all Sokal risk groups.

The overall best rate of BCR-ABL £ 0.0032% (equivalent to complete molecular response, CMR) was superior for nilotinib 300 mg bid (21%, \( P < .0001 \)) and nilotinib 400 mg bid (17%, \( P < .0001 \)) compared with imatinib (6%).

The overall best CCyR rate was superior for nilotinib 300 mg bid (85%, \( P < .01 \)) and nilotinib 400 mg bid (82%, \( P = .017 \)) compared with imatinib (74%).

The superior efficacy of nilotinib was further demonstrated using the 2009 European LeukemiaNet (ELN) 12-month milestone in which fewer patients had suboptimal response or treatment failure on nilotinib 300 mg bid (2%, 3%) and nilotinib 400 mg bid (2%, 2%) vs imatinib (11%, 8%).

Rates of progression to AP/BC on treatment were significantly lower for nilotinib 300 mg bid (0.7%, \( P = .006 \)) and nilotinib 400 mg bid (0.4%, \( P = .003 \)) compared with imatinib (4.2%).

The rate of progression on treatment was also significantly lower for nilotinib when including clonal evolution as a criteria for progression. There were fewer CML-related deaths on nilotinib 300 mg bid (n = 2), and 400 mg bid (n = 1) vs imatinib (n = 8).

Estimated OS rate (including data from follow-up after discontinuation) at 18 months was higher for nilotinib 300 mg bid (98.5%, \( P = .28 \)) and...
<table>
<thead>
<tr>
<th>Patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP)</th>
<th>18 months</th>
<th>CCyR MMR PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib 100 mg once daily (n=259) versus Imatinib 400 mg once daily (n=260)</td>
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</table>

After a minimum of 12 months (mos) of follow-up, dasatinib 100 mg once daily demonstrated significantly higher and faster rates of complete cytogenetic response (CCyR) and major molecular response (MMR) compared to imatinib 400 mg once daily.

The rate of confirmed CCyR by 18 mos continued to be higher for dasatinib than for imatinib (78% vs 70%); P=0.0366).

Based on time-in-cCCyR (a measure of durability) analysis involving all randomized pts, dasatinib-treated pts were 28% less likely to experience a progression event (as defined by European LeukemiaNet 2006) after achieving a cCCyR or never achieving a cCCyR compared to those on imatinib.

The MMR rate at any time was superior for dasatinib compared to imatinib (57% vs 41%, P=0.0002).

Based on time-to-response analysis, pts on dasatinib were 1.84-fold more likely to achieve a MMR than those on imatinib (HR=1.84, P <0.0001).

Rates of cCCyR in dasatinib-treated pts with low, intermediate and high risk were 92, 71 and 73%, respectively. The corresponding rates in the imatinib arm were 72, 71 and 64%.

Rates of MMR in dasatinib-treated pts with low, intermediate and high risk were 63, 56 and 51%, respectively. The corresponding rates in the
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients with newly diagnosed chronic myeloid leukemia in chronic phase</th>
<th>12 months</th>
<th>MMR</th>
<th>CCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib mesylate 800 mg/d</td>
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<td>(400 mg twice daily) n=319</td>
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<td>versus</td>
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<td>Imatinib mesylate 400 mg/d</td>
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<td>n=157</td>
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<tr>
<td>At 12 months, differences in MMR and complete cytogenetic response (CCyR) rates were not statistically significant (MMR, 46% v 40%; P = .2035; CCyR, 70% v 66%; P = .3470). However, MMR occurred faster among patients randomly assigned to imatinib 800 mg/d, who had higher rates of MMR at 3 and 6 months compared with those in the imatinib 400-mg/d arm (P = .0035 by log-rank test). CCyR also occurred faster in the 800-mg/d arm (CCyR at 6 months, 57% v 45%; P = .0146). The most common adverse events were edema, gastrointestinal problems, and rash, and all were more common in patients in the 800-mg/d arm. Grades 3 to 4 hematologic toxicity also occurred more frequently in patients receiving imatinib 800 mg/d.</td>
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<td>JE Cortes et al, 2010</td>
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<thead>
<tr>
<th>Therapy</th>
<th>Patients with pre-treated Philadelphia chromosome-positive, BCR-ABL-positive chronic myeloid leukemia (n=227)</th>
<th>n/a</th>
<th>HR</th>
<th>CR</th>
<th>MR</th>
<th>Toxicity</th>
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<tbody>
<tr>
<td>Standard-dose imatinib arm (400 mg/day)</td>
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<td>versus</td>
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<tr>
<td>High-dose imatinib arm (800 mg/day for 6 months followed by 400 mg/day as maintenance therapy)</td>
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<td>Compared to the standard-dose, high-dose imatinib led to higher rates of major and complete cytogenetic responses at both 3 months (major: 21% versus 37%, P=0.01; complete: 6% versus 25%, P&lt;0.001) and 6 months (major: 34% versus 54%, P=0.009; complete: 20% versus 44%, P&lt;0.001). This was paralleled by a significantly higher major molecular response rate at 6 months in the high-dose imatinib arm (11.8% versus 30.4%; P=0.003). At 12 months, the rates of major cytogenetic response (the primary end-point) were comparable between the two arms (57% versus 59%). In contrast to non-hematologic toxicities, grade 3/4 hematologic toxicities were more common in the</td>
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<td>Petzer AL et al, 2010</td>
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</table>
Cumulative complete cytogenetic response rates were higher in patients without dose reduction in the high-dose arm (61%) than in the patients with no dose reduction in the standard-dose arm (36%) (P=0.014).

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patients</th>
<th>24 month CCyR</th>
<th>MMR</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label oral Bosutinib 500 mg/d (n = 250) versus Imatinib 400 mg/d (n = 252)</td>
<td>Newly diagnosed chronic phase chronic myeloid leukemia stratified by Sokal score risk group (low, medium, high)</td>
<td>79%</td>
<td>55% (bosutinib) vs 45% (imatinib)</td>
<td>Faster for bosutinib (12.7 vs 24.6 wk)</td>
<td>Faster for bosutinib (36.9 vs 72.3 wk)</td>
</tr>
<tr>
<td>Transformation to AP/BP CML while on treatment occurred in 4 (2%) pts on bosutinib and 13 (5%) pts on imatinib.</td>
<td>On-study deaths from any cause occurred in 6 (2%) pts receiving bosutinib versus 13 (5%) pts receiving imatinib, and included 5 (2%) and 9 (4%) pts, respectively, who died due to CML progression.</td>
<td>Median on-treatment EFS and overall survival were not yet reached for either arm. At 18 mo, the Kaplan-Meier estimates of EFS were 95% for bosutinib versus 91% for imatinib, and the estimates of overall survival were 99% versus 95%, respectively.</td>
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<td>Imatinib monotherapy 800 mg daily (arm A) versus IM 800 mg combined with 2 successive cycles of daily cytarabine 200 mg/m² in 1-2 hours infusion for 7 days (arm B), followed by Imatinib monotherapy</td>
<td>Newly diagnosed CML patients between the age of 18 and 65 years in first chronic phase &lt;= 2 months (n=110)</td>
<td>31 months (range, 0-57)</td>
<td>MMR PFS OS Toxicity</td>
<td>High dose IM (600 or 800 mg) showed significantly higher molecular response rates than 400 mg in a dose escalation study of the combination of IM and cytarabine. The proportion of patients who achieved a MMR at 12 months was similar between the two treatment arms; 51% in arm A and 47% in arm B. PFS at 48 months was 91% in both treatment arms (p = 0.80). OS at 48 months was 100% in arm A and 92% in arm B.</td>
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<tr>
<td>Imatinib 800 mg/d (n = 338) versus imatinib 400 mg/d (n = 325), versus Imatinib 400 mg/d plus interferon alfa (n = 351).</td>
<td>Newly diagnosed CP-CML patients (n=1014)</td>
<td>12 Months</td>
<td>MMR Survival</td>
<td>A higher rate of MMR at 12 months occurred with tolerability-adapted imatinib 800 mg/d than with imatinib 400 mg/d (59% vs 44%) or imatinib 400 mg/d plus IFN (59% vs 46%). Independent of treatment approach, MMR at 12 months showed better progression-free survival (99% vs 94%) and overall survival (99% vs 93%) at 3 years when compared with 1% on the international scale or no MMR but showed no difference in 0.1% to 1% on the international scale, which closely correlates with complete cytogenetic remission.</td>
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<tr>
<td>Dasatinib (DAS) 100 mg versus Imatinib (IM) 400 mg</td>
<td>Newly diagnosed chronic-Phase chronic myeloid leukemia (n=253)</td>
<td>3 years</td>
<td>CCyR MMR PFS EFS</td>
<td>The proportion of patients achieving a complete cytogenetic remission rate was superior with DAS (84% vs 69%), as was the 12-month molecular response by the proportions of patients achieving &gt; 3-log, &gt; 4-log, and &gt; 4.5-log reduction in BCR-ABL transcript levels. Overall and progression-free survival was similar in the 2 arms. Among patients who achieved hematologic CR, 3-year relapse-free survival was 91% with DAS and 88%.</td>
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</tbody>
</table>
Dasatinib 100 mg (n = 259) versus Imatinib 400 mg (n = 260) once daily

Patients with newly diagnosed chronic-phase (CP) CML (n = 519) 24 Month (CCyR) and MMR

Cumulative cytogenetic response rates by 24 months for dasatinib versus imatinib, respectively, were CCyR in 86% versus 82% and cCCyR in 80% versus 74%.

The cumulative MMR rate by 24 months was 64% for dasatinib versus 46% for imatinib, and median time to MMR was 15 versus 36 months.

Hagop M. Kantarjian et al, 2012

Standard dose of imatinib (400 mg/day; n=113) versus 6 months of high-dose induction with imatinib (800 mg/day) followed by a standard dose of imatinib as maintenance therapy (n=114).

Pre-treated patients with chronic myeloid leukemia in chronic phase (n=227) n/a CCR MMR Survival

The rates of major and complete cytogenetic responses were significantly higher in the high-dose arm than in the standard-dose arm at both 3 and 6 months. Major cytogenetic responses: 36.8% versus 21.2% and 50.0% versus 34.5%. Complete cytogenetic responses: 22.8% versus 6.2% and 40.4% versus 16.8%.

At 12 months, the difference between treatment arms remained statistically significant for complete cytogenetic responses (40.4% versus 24.8%) but not for major cytogenetic responses (49.1% versus 44.2%).

The rate of major molecular responses was also significantly better at 3 and 6 months in the high-dose arm (month 3: 14.9% versus 3.5%; month 6: 32.5% versus 8.8%).

Overall and progression-free survival

Andreas L. Petzer et al, 2012

Grade 3 and 4 toxicities were most commonly hematologic, including thrombocytopenia in 18% and 8% of DAS and IM patients, respectively.

DAS induced more complete cytogenetic response and deeper molecular responses after 12 months, compared with IM 400 mg, and with a median follow-up of 3.0 years there have been very few deaths, relapses, or progressions in the 2 arms.

In summary, DAS compared with IM appeared to have more short-term cytogenetic and molecular response, more hematologic toxicity, and similar overall survival.
Imatinib versus Nilotinib

| Patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) | 3 years | MMR | Major molecular response, molecular response of BCR-ABL \(\leq 0.01\%\) expressed on the international scale (BCR-ABL<sup>IS</sup>) and BCR-ABL<sup>IS</sup> 0.0032% (MR<sup>4.5</sup>) rates were significantly higher with nilotinib compared with imatinib.

Differences in the depth of molecular response between nilotinib and imatinib have increased over time.

Nilotinib was associated with a significantly lower probability of progression to accelerated phase/blast crisis vs imatinib (two (0.7%) progressions on nilotinib 300 mg twice daily, three (1.1%) on nilotinib 400 mg twice daily and 12 (4.2%) on imatinib).

When considering progressions occurring after study treatment discontinuation, the advantage of nilotinib over imatinib in preventing progression remained significant (nine (3.2%) progressions on nilotinib 300 mg twice daily, six (2.1%) on nilotinib 400 mg twice daily and 19 (6.7%) on imatinib).

Both nilotinib and imatinib were well tolerated, with minimal changes in safety over time. Nilotinib continues to demonstrate superior efficacy in all key response and outcome parameters compared with imatinib.

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**Table:**

<table>
<thead>
<tr>
<th>BCR-ABL&lt;sup&gt;IS&lt;/sup&gt;</th>
<th>CCyR</th>
<th>OMR</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>MMR 50% major molecular responses (MMR) at 18 months</td>
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<tr>
<td>Imatinib (IM) 400 mg daily provides 50% major molecular responses (MMR) at 18 months</td>
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</table>

At 3 Mo, 88% of pts achieved complete haematological response.

MMR rates at 6 and 12 Mo were higher for IM-PegIFN as compared to IM-400 (p<10-3).

At 18 MO the cumulative OMR rates were 22% (IM-400), 28% (IM-600),...
mg/m<sup>2</sup>/d, d15-28 of 28-day cycles)(n=158)

versus

IM 400 mg/d combined to s/c Peg-IFN2alpha (90 mug/wk) (n=159)

25% IM-1ra-c), 43% (IM-PegIFN).

Grade 3/4 neutropenia and/or thrombocytopenia occurred during the first year in 8% IM-400, in 14% IM-600, in 41% IM-Ara-C and in 40% IM-PegIFN arms respectively.

Grade 3/4 non-haematological toxicities occurred in 19% IM-400 (oedemas, muscle cramps), in 30% IM-600, in 27% IM-Ara-C (diarrhoea) and in 31% IM-PegIFN pts (skin rashes, asthenia). Within the first 12 Mo, discontinuation of experimental treatment occurred in 8% IM-600, 39% IM-Ara-C and in 45% IM+PegIFN pts

Abbreviations: CCyR = Complete Cytogenic Response; EFS = Event Free Survival; PFS = Progression Free Survival; OS=Overall survival; MMS = Major Molecular Response; AEs = Adverse Events

Clinical Expert Interest Declaration:
No potential conflict of interest was declared by the clinical expert

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. 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? YES

2. On initial review,
   a. Does the newly identified evidence support the existing recommendations? A. NO
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? B. NO

3. 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 NO
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?

NO. A new document called “Targeted therapy for CML” will be started as soon as resources will become available.

Review Outcome
ARCHIVED

DSG/GDG Approval Date
November 7, 2013

DSG/GDG Commentary

New References Identified (alphabetic order):


Tim P. Hughes, M.D., Jaspal Kaeda, Ph.D., Susan Branford, Zbigniew Rudzki, Ph.D., Andreas Hochhaus, M.D., Martee L. "Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia." New England Journal of Medicine 349(15): 1423-1432.


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3. DELAY – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

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