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Practice Guideline Report 6-15 IN REVIEW

Treatment of Chronic Myeloid Leukemia with Imatinib

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

Report Date: July 16, 2004

An assessment conducted in November 2012 placed Practice Guideline (PG) 6-15 IN REVIEW. This means that it is undergoing a review for currency and relevance. The Hematology Disease Site Group (DSG) has determined that it is still appropriate for this document to continue to be available while this updating process unfolds.

PG 6-15 consists of a Summary and a Full Report and is available on the CCO website (http://www.cancercare.on.ca) PEBC Hematology DSG page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/hema-ebs/

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Treatment of Chronic Myeloid Leukemia with Imatinib
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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:
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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.[1] 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:
[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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