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CED-CCO Advice Report 6-23 EDUCATION AND INFORMATION 2012

Dasatinib for the Treatment of Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia

I. Walker, A.E. Haynes, and C.T. Kouroukis

Report Date: June 2007

This CED-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol). The report, which consists of a Summary and a Full Report, is available on the CCO web site (http://www.cancercare.on.ca).

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

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Dasatinib for the Treatment of Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia

I. Walker, A.E. Haynes, and C.T. Kouroukis

Report Date: June 2007

The 2007 guideline recommendations were put 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.

SUMMARY

Question

Does dasatinib, alone or in combination with other drugs, improve outcomes in patients with chronic myeloid leukemia (in chronic, accelerated, or blastic phases) in whom primary standard therapy with imatinib has failed, either as a result of resistance or intolerance?

- Outcomes of interest include survival, quality of life, duration of treatment response, toxicity, hematological response, and cytogenetic or molecular response.

Target Population

These recommendations apply to adult patients with imatinib-resistant or –intolerant CML in chronic phase, accelerated phase, or blast crisis.

Recommendations

- **Dasatinib is recommended for patients with CML in chronic phase who have primary or acquired resistance to high dose imatinib (600 mg/day).**

  Key Evidence

  - One randomized controlled trial (RCT) compared dasatinib 140 mg (70 mg twice daily) to imatinib 800 mg (400 mg twice daily) in patients with chronic phase CML who were resistant to imatinib 400 – 600 mg (1).
  - With 15 months of follow up, the dasatinib arm had statistically significant higher rates of major cytogenetic response (MCyR), complete cytogenetic response (CCyR), complete hematological response (CHR), and major molecular response (1).

- Progression-free survival was significantly higher in the dasatinib arm compared to the imatinib arm (93% versus 54%, respectively; hazard ratio [HR], 0.14, 95% confidence interval [CI], 0.05 to 0.40) (1). In addition the median time to treatment failure was significantly higher in the dasatinib arm (not yet reached versus 3.5 months; HR, 0.16, 95% CI, 0.10 to 0.26) (1).

- **Dasatinib is recommended for patients with CML that has progressed to accelerated phase or blast crisis while on imatinib.**

  Key Evidence

  - One randomized trial (2) comparing two doses of dasatinib in patients with advanced phase CML and three single arm trials (3-5) of dasatinib in patients with CML in accelerated phase have reported response rates of:
    - MCyR: 27% to 40%
    - CCyR: 18% to 29%
    - CHR: 31% to 45%
  - Two single arm trials (3,6) of dasatinib in patients with CML in myeloid (MBC) or lymphoid blast crisis (LBC) have reported response rates of:
    - MCyR: LBC 50% to 80%; MBC 31% to 35%
    - CCyR: LBC 30% to 43%; MBC 26% to 27%
    - CHR: LBC 26% to 70%; MBC 26% to 35%

- **Dasatinib is recommended for patients with CML in chronic phase who are intolerant to the recommended starting dose of imatinib of 400 mg/day or to those who are intolerant to a dose of 600 mg/day, required because of failure to achieve targets of therapy or who are in accelerated phase or blast crisis.**

  Key Evidence

  - Two randomized trials (2,7) that compared different doses of dasatinib and six single arm trials included patients with imatinib-intolerant CML in chronic phase (one trial) (8), accelerated phase (one trial) (5), blast crisis (one trial) (6), or any phase (three trials) (3,4,9).
  - Hochhaus et al (8) included 59 patients with imatinib-intolerant CML in chronic phase of a total of 186 patients with either resistance or intolerance. A MCyR was observed in 80% of patients, CCyR in 64%, and CHR in 97%. Of the 57 patients who obtained a CHR only one patient subsequently progressed. In addition, the authors reported that dasatinib was well tolerated. At eight months follow-up only 16 patients out of 186 discontinued treatment as a result of adverse events. The authors also reported that the incidences of adverse events were comparable for patients with imatinib-resistant and –intolerant chronic phase CML.
  - Cortes et al (6) reported that six of 74 patients in myeloid blast crisis were imatinib-intolerant at enrolment. Three of those achieved an overall hematological response of whom one had a major hematological response. None experienced disease progression. In addition, five of 42 patients in lymphoid blast crisis were imatinib-intolerant at enrolment. Two of those achieved a major hematological response. None of those patients experienced disease progression.

- **The recommended starting dose of dasatinib is 100 mg once daily for patients in chronic phase and 140 mg daily for those in accelerated phase or blast crisis.**

Key Evidence

- One randomized trial (7) comparing four doses of dasatinib in patients with chronic phase CML reported no significant differences in the rates of CHR, MCyR, or CCyR. However, the dasatinib 100 mg once daily arm had significantly lower rates of grade III or IV neutropenia and thrombocytopenia as well as any grade pleural effusion compared to dasatinib doses of 50 mg twice daily, 70 mg twice daily, and 140 mg once daily.
- One randomized trial (2) comparing two dosing schedules of dasatinib (70 mg twice daily versus 140 mg once daily) in 398 patients with CML in either accelerated phase or blast crisis reported similar rates of CHR, MCyR, and CCyR. However, the dasatinib 140 mg once daily arm had significantly lower rates of any grade pleural effusions and peripheral edema.

Qualifying Statements

Failure of imatinib therapy, the indication for dasatinib therapy, is defined as one or more of the following:

1. The presence of grades III or IV non-hematological toxicity or clinical intolerance to lower grades of toxicity.
2. Failure to attain initial targets on 400 mg/day of imatinib and not subsequently responding to an increase of imatinib to 600 mg daily, targets being:
    a. Complete hematologic remission at 3 months.
    b. Any cytogenetic response at 6 months.
    c. A major cytogenetic response at 12 months.
    d. A complete cytogenetic response at 18 months.
3. Loss of previously attained targets or a significant increase in *BCR-ABL* transcripts (≥ 0.5 log from best response).
4. Progression to accelerated phase or blast crisis and failing to respond to an increased dose of imatinib of at least 600 mg.

Definitions of endpoints/targets of initial therapy:

- CHR (chronic phase)
    - White blood count (WBC) ≤ upper limit of normal (ULN)
    - Platelets < 450,000/mm^3
    - No blasts or promyelocytes in peripheral blood
    - < 5% myelocytes plus metamyelocytes in peripheral blood
    - Basophils in peripheral blood < 20%
    - No extramedullary involvement (including no hepatomegaly or splenomegaly)

- CHR (accelerated phase/blast crisis)
    - WBC < ULN
    - Absolute neutrophil count (ANC) ≥ 1000/mm^3
    - Platelets ≥ 100,000/mm^3
    - No blasts or promyelocytes in peripheral blood
    - Bone marrow blasts ≤ 5%
    - < 5% myelocytes plus metamyelocytes in peripheral blood
    - Basophils in peripheral blood < 20%
    - No extramedullary involvement (including no hepatomegaly or splenomegaly)

- CCyR
    - 0% Ph-positive cells in metaphase in bone marrow

- Partial cytogenetic response (PCyR)
  - 1% to 35% Ph-positive cells in metaphase in bone marrow

- MCyR
  - CCyR + PCyR
  - ≤ 35% Ph-positive cells in metaphase in bone marrow

- Major molecular response (MMoR)
  - ≥ 3 log suppression of *BCR-ABL* transcripts from baseline

- Complete molecular response (CMoR)
  - Undetectable levels of *BCR-ABL transcripts* (usually ≥ 4 – 4.5 log suppression from baseline.

Related Guidelines

Practice Guideline #6-15: Treatment of Chronic Myeloid Leukemia with Imatinib.

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Contact Information

For further information about this special advice report, please contact:

Dr. K. Imrie, Co-Chair, Hematology Disease Site Group
Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5
Phone: 416-480-4757 Fax: 416-480-6002

or

Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group
Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2
Phone: 905-387-9711 ext. 62484 Fax: 905-575-6340

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

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FULL REPORT

I. QUESTION

Does dasatinib, alone or in combination with other drugs, improve outcomes in patients with chronic myeloid leukemia (in chronic, accelerated, or blastic phases) in whom primary standard therapy with imatinib has failed, either as a result or resistance or intolerance?

- Outcomes of interest include survival, quality of life, duration of treatment response, toxicity, hematological response, and cytogenetic or molecular response.

II. CHOICE OF TOPIC AND RATIONALE

Chronic myeloid leukemia (CML), with its classical Philadelphia chromosome marker, is caused by a fusion protein, BCR-ABL, the product of an abnormal chimeric gene formed by translocation of a portion of the *ABL* gene on chromosome 9 to a region adjacent to a portion of the *BCR* gene on chromosome 22. The normally regulated tyrosine kinase activity of the ABL protein, a product of the normal autosome, is then usurped by the dysregulated BCR-ABL protein of the Philadelphia chromosome (1). Transfection of mice with the *BCR-ABL* gene results in chronic myeloid leukemia (2), confirming the central role of the *BCR-ABL* gene in the pathogenesis.

The clinical course of CML progresses through chronic, accelerated, and blastic phases, with consequent worsening prognosis, the latter phases being relatively short in most cases. The median survival of patients receiving minimal or no treatment is four to five years (3).

Randomized trials conducted over thirty years have demonstrated improved survivals with successive new therapies (3-10). The recent introduction of an agent, imatinib (Gleevec®), which relatively specifically inhibits the tyrosine kinase activity of BCR-ABL has revolutionized the treatment of chronic myeloid leukemia; survival is dramatically improved and the frequency of serious side effects low. Imatinib has now had at least five years of formal evaluation and while the results of therapy with this agent have been remarkable not all patients benefit (11). Side effects can result in discontinuation of therapy, both by those few patients having serious side effects and by those who find less serious side effects intolerable when experienced over long time periods.

While the overall survival of patients on imatinib is unprecedented this drug is not a cure; *BCR-ABL* transcripts or overt CML recur in most patients when the drug is discontinued. Therefore, there remains the potential for relapse, even in patients who have had a complete response. Development and evaluation of new tyrosine kinase inhibitors is therefore needed for those who fail imatinib therapy whether due to drug resistance or side effects.

New kinase inhibitors that are available for clinical use at present are dasatinib (Sprycel®; Bristol-Myers Squibb, Princeton, New Jersey), which has received Notice of Compliance (Health Protection Branch, Health Canada) and is the topic of this review, and nilotinib, which is in a late stage of pre-licensure evaluation.

Two issues central to the issue of side effects and drug resistance are, firstly, the incomplete specificities of the tyrosine kinase inhibitors toward BCR-ABL and, secondly, mutations in BCR-ABL, most particularly at the active site, that confer drug resistance (12). The incomplete specificity of inhibitors toward BCR-ABL relates to inhibition by all three drugs of some of the many other human tyrosine kinases, there being 58 of the receptor type and 32 of the cytoplasmic type (www.expasy.org). In addition to inhibiting BCR-ABL, imatinib and nilotinib inhibit PDGFR and Kit, while dasatinib inhibits also the Src family of kinases, Kit, PDGFR, and ephrin A receptor kinase. Side effects of these drugs could conceivably relate to inhibition of some or all of these enzymes. Drug resistance to imatinib is attributable to various mechanisms

including increased expression of *BCR-ABL* through gene amplification, decreased intracellular imatinib concentrations caused by drug efflux proteins, imatinib binding by plasma proteins, and clonal evolution; however many cases are caused by mutations in the BCR-ABL protein that prevent imatinib binding. Dasatinib effectively inhibits all imatinib-resistant kinase domain mutations tested, with the exception of T315I and, unlike imatinib, is not a substrate of multidrug resistance protein-1 (MDR1) (12).

Currently Recommended Drug Therapy for Chronic Myeloid Leukemia

The Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC) Hematology Disease Site Group (DSG) recommends imatinib (Gleevec®) as first-line treatment for newly diagnosed patients with Philadelphia-positive chronic myeloid leukemia (13). This recommendation, which dates from July 2004, was supported by the conclusions of a simultaneous publication from the National Institute for Clinical Excellence (NICE; UK) (14), and more recently by European LeukemiaNet (15). The Cancer Care Ontario recommendation for Gleevec remains current and reflects Canadian practice (16).

Specifically, the recommendations of the CCO-PEBC Hematology DSG Practice Guideline Report #6-15 (13) state:

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.*

Long Term Follow Up of Imatinib Therapy since CCO Recommendations

Evidence leading to the adoption of imatinib as recommended first line therapy was dominated by results of the IRIS trial in which imatinib was compared with the combination of interferon and cytarabine, the existing recommended therapy. The trial was originally published with a median follow up of 19 months, and a 60-month follow up has now been published (11). Of the 553 patients randomized to imatinib 69% have remained on therapy and overall survival is 89% (92% when censored at bone marrow transplantation). Ninety-three percent (93%) of patients have been free of progression to accelerated phase or blast crisis. There were two important additional observations: Firstly, the rate of progression to accelerated phase or blast crisis was lower in the fourth and fifth years (0.9% and 0.6% respectively) than in each of the first three years (1.5%, 2.8%, and 1.6% respectively), indicating that initial responses have been durable; secondly, failure to achieve a major cytogenetic response (either complete or partial) at one year was a predictor for subsequent progression to accelerated phase or blast crisis (3% and 7% for complete and partial responders, 19% for the remainder). The difference between complete and partial responders was not statistically significant but the difference between either of these responders and those remaining was highly statistically significant ($p<0.001$).

Endpoints in Clinical Trials of CML Therapy

Potential endpoints include survival and progression to accelerated phase or blast crisis. Laboratory endpoints include cytogenetic and molecular responses. Survival is the most important endpoint in CML; however a survival advantage of imatinib could not be demonstrated in the IRIS trial. The trial design did not include survival as an endpoint and, further, 65% of interferon treated patients had crossed over to imatinib by 60 months and only 3% of patients remained on this therapy. In the absence of information on survival from randomized trials, two retrospective cohort comparison studies have been performed, both finding improved survival with imatinib compared to interferon/cytarabine (17,18). These two studies are important in providing the only information ever likely to become available on the impact on survival of imatinib compared with interferon-based therapy. Though these studies were not randomized the findings are consistent. Furthermore the cohorts used by Roy et al (18) for their comparison had previously been well defined, having been arms of previous randomized trials.

The high survival rate in CML lead to adoption of a composite endpoint, consisting of either death or progression to accelerated or blast crisis, both of the latter events resulting in a subsequent high mortality. In the IRIS trial all patients achieving both a complete cytogenetic response (0% Philadelphia-positive [Ph+] cells) and a major molecular response (>3 log suppression) at 18 months continued in chronic phase without accelerated phase or blast crisis thereafter. However, even those who achieved a complete cytogenetic response at 18 months, but lacked a major molecular response had only a 2% likelihood of accelerated phase or blast crisis, and this difference was not significant. Overall, 99% of all patients achieving a major cytogenetic remission at twelve months continued without AP/BC regardless of molecular response, while if only a partial response was achieved (<35% Ph+ cells) 10% of patients progressed to AP or BC.

Table 1 summarizes the likelihood of long-term event free survival of the 553 patients randomized to imatinib on the IRIS study as predicted by the attainment of various end-points at different time periods. The data are taken from three follow up reports of this study (11,19,20).

Table 1. Percentage of subjects randomized to imatinib on the IRIS trial having long term Event Free Survival (EFS) according to degree of cytogenetic and molecular responses.

End points		Event-free survival		
Type	**Response**	**6 months %**	**12 months %**	**18 months %**
Cytogenetic response	**Complete**	95 [1]	97 [3]	99 [3]
	Partial	NR	93 [3]	90 [3]*
	Minimal or None	75 [1]*†	81 [3]*	83 [3]*
Molecular response	**Complete**	NR	100 [2]	100 [3]
	Major	NR	NR	98 [3]
	Minor	NR	93 [2]*	87 [3]*

Notes: %=percent of subjects that obtained a specific response with long term EFS ([1]at 24 months; [2]at 30 months; [3]at 60 months) out of all subjects that obtained that same specific response; *=statistically significantly inferior to best result; †=significant only for 'no response' (Ph= cells >95%); Molecular responses are those in subjects having Complete or Partial cytogenetic responses.

Present Status of CML Therapy

1. Imatinib is recommended as first line therapy and is being used for nearly all patients. Bone marrow transplantation is now being used less and less often (10 cases in Ontario in 2005; http://www.cbmtg.org).
2. Patients given imatinib as first-line therapy have a likelihood of survival of 90% at five years.
3. Serious side effects are infrequent.

4. Clinical trials of imatinib have established that the attainment of a major cytogenetic response predicts freedom from progression of chronic phase to accelerated phase, blast crisis, or death. A major cytogenetic response is therefore the most important marker of prognosis for those in chronic phase and a surrogate endpoint for survival.
5. At five years only 69% of patients remain on imatinib; in the absence of new and effective therapy the long term survival of the nearly one third of patients discontinuing imatinib is of concern.
6. New therapies are needed to treat patients who fail imatinib therapy as there are currently no other treatment options.
7. Dasatinib is a new tyrosine kinase inhibitor that has undergone clinical trials and has received Notice of Compliance; no other drug is presently available for consideration of funding. Nilotinib is an investigational tyrosine kinase inhibitor that is being evaluated in clinical trials.

III. METHODS

This advice report, produced by the PEBC, is a convenient and up-to-date source of the best available evidence on the role of dasatinib in the treatment of imatinib-resistant or –intolerant CML developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

Literature Search Strategy

A systematic search of the published literature identified all reports relating to the use of dasatinib for the treatment of patients with imatinib-resistant or –intolerant CML. The MEDLINE (1950 to April Week 1, 2007), EMBASE (1980 to 2007, Week 15 [April 17]), MEDLINE Daily Update (April 2007), MEDLINE In-Process & Other Non-Indexed Citations (April 2007), and the Cochrane Library (2007, Issue 2) databases were searched according to the strategy shown in Appendix 1. Abstracts from the American Society of Hematology (ASH) (2004-2006) and the American Society of Clinical Oncology (ASCO) (2004-2007) annual conference proceedings were also searched. Our search strategy included only studies published in English. Publications evaluating dasatinib in non-human subjects and those that were categorized as "published comments," "letters," "notes," "books," and "editorials" were excluded. The National Cancer Institute (NCI) Clinical Trials Register, the United States National Institutes of Health (NIH) Clinical Trials, and the European Organization for Research and Treatment of Cancer (EORTC) databases were searched to identify ongoing clinical trials. The National Guidelines Clearinghouse and the CMA Infobase were searched for clinical practice guidelines. The references for all selected articles were also reviewed. Where it was deemed necessary, the authors of included publications were contacted to obtain missing or additional data.

Relevant articles and abstracts were selected and reviewed by two reviewers (IW and AH), and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies were prospective phase I, II, or III clinical trials.

2. Studies included adult patients with CML (in any phase) who failed primary standard therapy with imatinib.
3. Studies tested the role of dasatinib, either as a single agent or in combination with other therapy.
4. For comparative trials, dasatinib was compared with any agent, any combination of agents, or placebo.
5. Results were reported for any of the following outcomes: overall survival, quality of life, hematological response, cytogenetic or molecular response, duration of treatment response, and toxicity.
6. Studies were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed the use of dasatinib in patients with CML that is resistant or intolerant to imatinib.

Exclusion Criteria

1. Studies with less than 10 patients.
2. Reports published in a language other than English.
3. Letters, editorials, notes, comments, and books.
4. Studies with a primary outcome other than the clinical efficacy of dasatinib (as measured by overall survival, quality of life, hematological response, cytogenetic or molecular response, and duration of treatment response).

Synthesizing the Evidence

Due to a lack of adequately designed RCTs and the heterogeneity that exists between the different study populations pooling of study results was deemed inappropriate.

IV. RESULTS

Literature Search Results

A total of 218 citations were retrieved from the MEDLINE, MEDLINE Daily Update, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, and the Cochrane Library databases. Four citations met the inclusion criteria. In addition, 21 abstracts from the conference proceedings of ASH or ASCO were identified that met inclusion criteria. After reviewing reference lists of the relevant citations, one addition publication was identified that met inclusion criteria (a Blood First Edition Paper, pre-published online). Many of the identified abstracts were of trials that have since been fully published or for which more up-to-date abstracts were available. Only the full publication or most up-to-date abstract has been referenced for each trial. In total, 10 studies of dasatinib in imatinib-resistant or –intolerant CML were identified. One study was pre-published online, four were fully published , and five were available only as abstracts. The remaining study was a phase I trial, published in abstract form only, that did not provide sufficient outcome data to meet inclusion criteria (21). That trial was added to the ongoing trials section and is not discussed further. Two of the identified abstracts were of systematic reviews that looked at grade III or IV adverse events of nilotinib and dasatinib in patients with chronic phase CML (22) or accelerated phase CML (23). No evidence-based guideline documents were identified.

Systematic Reviews

Two systematic reviews of dasatinib were identified. The first compared the rates of grade III or IV adverse events in patients with chronic phase CML that received dasatinib 70 mg twice daily (BID) to those who received nilotinib 400 mg BID (22). The second also compared the rates of grade III or IV adverse events, but in patients with accelerated phase CML who received nilotinib or dasatinib as in the first systematic review (23). Neither abstract provided a search strategy. Both studies reported that the rates of non-hematological grade III or IV

adverse events were higher in patients that received dasatinib. In addition, the rates of grade III or IV hematological adverse events were 1.8 to 2.6 times higher (23) for accelerated phase patients that received dasatinib compared to nilotinib and they were approximately two times higher for chronic phase patients who received dasatinib compared to nilotinib (22) (Table 2). However, the statistical methods used to compare the rates were not provided, nor were p-values.

Table 2. Rates (range) of grade III or IV hematological adverse events in two systematic reviews.

Author (ref)	Phase	Intervention	N	Anemia (%)	Neutropenia (%)	Thrombocytopenia (%)
Carpiuc, 2007 (22) abstract	Chronic	nilotinib	NR	7.5 (5.3 – 9.9)	26.4 (13.1 – 33.1	24.7 (19.9 – 32.9)
		dasatinib	NR	18.0 (9.0 – 20.0)	49.0 (36.4 – 58.0)	48.0 (35.0 – 54.0)
Snedecor, 2007 (23) abstract	Accelerated	nilotinib	NR	27.1 (13.5 – 30.4)	41.4 (14.6 – 43.8)	35.6 (28.0 – 39.4)
		dasatinib	NR	70.0 (67.3 – 80.0)	74.0 (71.0 – 81.8)	83.0 (79.4 – 83.0)

Notes: NR, not reported; ref, reference.

Trial Characteristics and Quality

Of the nine trials eligible for inclusion in this systematic review, three were randomized controlled trials (RCT) and six were non-comparative single-arm phase I or II trials. Patient details and study characteristics can be found in Table 3. One RCT, reported by Kantarjian et al (24), was prepublished online by *Blood* and enrolled patients with chronic phase CML who were resistant or intolerant to 400 mg or 600 mg doses of imatinib. That trial was the only RCT to compare dasatinib to a standard therapy; patients were randomized, in a 2:1 ratio, to receive either dasatinib (70 mg BID) or imatinib (400 mg BID). The trial was open-label and no sample size calculation was provided. The authors reported a median follow-up of 15 months. Twenty-one patients initially randomized to receive dasatinib discontinued treatment either due to disease progression or intolerance. Fifteen patients in that treatment arm crossed-over to the imatinib arm. Thirty-nine patients initially randomized to receive imatinib discontinued treatment either due to a lack of response, disease progression, or intolerance. Thirty-nine of those patients crossed-over to the dasatinib arm. A further 14 patients discontinued treatment without crossing-over to the alternative treatment arm (one and 13 patients in the dasatinib and imatinib arms, respectively). The primary outcome was the rate of major cytogenetic response (MCyR) measured at 12 weeks. Secondary outcomes included MCyR or complete hematological response (CHR) at any time prior to crossover, duration of MCyR or CHR, time to MCyR or CHR prior to crossover, and time to treatment failure. Definitions of outcomes used in each study can be found in Appendix 2.

Table 3. Patient characteristics and intervention details for trials of dasatinib in CML.

Author (ref)	Patients	Treatment	N
Randomized Controlled Trials			
Comparison to standard therapy			
Kantarjian, 2007 (24)	CML in CP[A] with primary[B] or acquired[C] resistance to imatinib at doses of 400 mg to 600 mg	dasatinib 140 mg (70 mg bid)	101[D]
		imatinib 800 mg (400 mg bid)	49[D]
Dose-finding trials			
Shah, 2007 (25) abstract	CML in CP with resistance[B or C] or intolerance[E] to imatinib	dasatinib 50 mg bid	166
		dasatinib 100 mg qd	166
		dasatinib 70 mg bid	167
		dasatinib 140 mg qd	163
Pasquini, 2007 (26) abstract	CML in AP or BC or Philadelphia chromosome-positive ALL with resistance or intolerance to imatinib	dasatinib 70 mg bid	305
		dasatinib 140 mg qd	304
Non-comparative Trials			
Mixed phases			
Quintas-Cardama, 2007 (27)	CML that failed therapy with imatinib and nilotinib	dasatinib: 70 mg bid or 140 mg qd	23
Talpaz, 2006 (28)	CML[F] or Philadelphia chromosome-positive ALL, with hematologic resistance[G] or intolerance[H] to imatinib	dasatinib, (dose escalation) CP: 15 mg QD to 180 mg QD or 25 mg BID to 70 mg BID; Advanced phase: 35 mg BID to 120 mg BID	84
Quintás-Cardama, 2006 (29) abstract	CML resistant or intolerant to imatinib	dasatinib (dose escalation): 50 mg bid, 100 mg qd, 70 mg bid, or 140 mg qd	53
Blast crisis			
Cortes, 2007 (30)	CML in BC[I] resistant[J] to or intolerant[K] to imatinib, ECOG PS ≤ 2	dasatinib 70 mg bid orally	116
Accelerated phase			
Cortes, 2006 (31) abstract	CML in AP resistant to or intolerant to imatinib	dasatinib 70 mg bid orally	174
Chronic phase			
Hochhaus, 2007 (32)	CML in CP[L] resistant[B] or intolerant[E] to imatinib	dasatinib 70 mg bid orally	387

Notes: ALL, acute lymphoblastic leukemia; AP, accelerated phase, BC, blast crisis; bid, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; d, day; N, number of patients randomized or enrolled; NR, not reported; qd, once daily; ref, reference.

[A]CP was defined as < 15% blasts, < 20% basophils, and < 30% blasts plus promyelocytes in peripheral blood or bone marrow, platelet count ≥ $100x10^9$/L, and no extramedullary involvement.

[B]Primary resistance was defined as the absence of a complete hematologic response after three months of imatinib therapy, absence of any cytogenetic response after six months of treatment, or the absence of a major cytogenetic response (less than 35% Philadelphia chromosome-positive cells) after 12 months of treatment.

[C]Acquired resistance was defined as a relapse after a previous hematologic or major cytogenetic response.

[D]Randomized in 2:1 ratio (dasatinib:imatinib).

[E]Intolerance to imatinib was defined as grade ≥ 3 nonhematologic toxicity or grade 4 hematologic toxicity that persisted for more than seven days.

[F]CP was defined as in "A" above; BC was defined as ≥ 30% blasts in peripheral blood or bone marrow or extramedulllary leukemic infiltrates other than in the spleen or liver; AP was defined as not meeting the criteria for CP or BC.

[G]Hematologic resistance was defined as either primary (CP-absence of complete hematologic response after three months of imatinib 400 mg/d *or* white blood count ≥ $10x10^9$/L and rising on two consecutive measurements with at least one white blood count > $15x10^9$/L while taking imatinib 400 mg/d; AP-absence of major or minor hematologic response after three months of imatinib therapy) or acquired (CP-achieve a complete hematologic response *and* develop a white blood count ≥ $10x10^9$/L and rising on two consecutive measurements with at least one white blood count > $15x10^9$/L while taking imatinib 400 mg/d; AP-achieve a major or minor hematologic response while on imatinib and then progress).

[H]Intolerance to imatinib was defined as discontinuation of imatinib due to nonhematologic toxicity of any grade.

[I]Blast crisis defined as 30% or greater myeloid or lymphoid blasts in peripheral blood or bone marrow, or extramedullary leukemic infiltrates other than in the spleen or liver with peripheral blood blast cell morphology.

[J]Resistance to imatinib was defined as progression from CP to BC (at imatinib dose of 400 mg/d), AP to BC (at imatinib dose of 600 mg/d), or for de novo BC or PBC patient remained in BC after four weeks or more at imatinib dose of 600 mg/d.

[K]Intolerance to imatinib was defined as discontinuation of imatinib treatment due to toxicity related to an imatinib dose of 400 mg/d or less, or inability to tolerate a dose of >400 mg/d.

[L]CP was defined as < 15% blasts in peripheral blood and bone marrow, < 20% basophils in peripheral blood, < 30% blasts plus promyelocytes in peripheral blood and bone marrow, platelet count ≥ $100x10^9$/L (except if caused by recent therapy), and no extramedullary involvement other than in the spleen or liver.

The remaining two RCTs were reported in abstract form only and compared different doses of dasatinib. Shah et al (25) reported on an open-label trial that randomized 662 patients with chronic phase CML, resistant or intolerant to imatinib, to one of four doses of dasatinib (Table 3). The primary outcome of the study was to compare cytogenetic response rates at six months between patients who received twice daily BID doses (50 mg or 70 mg) to those who received once daily (QD) doses (100 mg or 140 mg). The authors planned a secondary analysis to compare safety between all of the treatment arms. Patient follow-up was a minimum of six months. The authors did not report on withdrawals and dropouts or provide a sample size calculation. Pasquini et al (26) reported on an open-label trial that randomized 611 patients with accelerated or blastic phase CML, resistant or intolerant to imatinib, to one of two doses of dasatinib: 70 mg BID or 140 mg QD. Data were provided for 609 patients; 305 were randomized to dasatinib 70 mg BID and 304 received dasatinib 140 mg QD. Patient follow-up was a median of 6.5 months and no sample size calculation was provided. In addition, the authors did not provide information on withdrawals, dropouts, or patient crossover.

The remaining trials were available as full publications (27,28,30,32) or in abstract form only (29,31) and all were single-arm non-comparative trials. One trial each enrolled patients with CML in blast crisis (30), accelerated phase (31), or chronic phase (32). Three trials enrolled patients with CML in any phase (27-29). Five trials reported on the length of follow-up: two reported median follow-up of 34 and 35 weeks (27,29), two reported minimum follow-up of nine and eight months (31,32), and one trial reported that follow-up ranged from one to 12 months (30). Of note, Hochhaus et al enrolled 387 patients; however, the authors reported that results were available only for the initial cohort of 186 patients (32).

Outcomes

Overall Survival

None of the trials reported data on overall survival.

Response

Response data for each trial can be found in Table 4.

Chronic phase

Kantarjian et al (24) reported no significant difference in the primary endpoint, which was the rate of MCyR at 12 weeks, (36% vs. 29%; p=0.4025). However, by the end of the trial (median follow up 15 months) the rate of MCyR for patients taking dasatinib (52%) became significantly higher than for those taking imatinib (33%)(p=0.023). Also significantly higher at the end of the trial, for dasatinib treated patients, were CHR (93% vs 82%; p=0.034), CCyR (40% vs 16%; p=0.004) and major molecular responses, defined as a ≥ 3 log decrease in *BCR-ABL* from baseline, (16% vs 4%; p=0.038). Of clinical significance were improvements, for patients taking dasatinib, in treatment failure (hazard ratio [HR], 0.16; 95% confidence interval [CI], 0.10 to 0.26; p<0.0001) and progression free survival (HR, 0.14; 95% CI, 0.05 to 0.40; p<0.0001).

Shah et al (25) reported similar rates of CHR in patients with chronic phase CML randomized to one of four doses of dasatinib; responses ranged from 87% to 93%. The authors also reported that the rates of MCyR and CCyR were similar between each arm of the study (Table 4).

Table 4. Trials of dasatinib in CML: efficacy outcomes.

Author (ref)	Treatment	N (rand/ eval)	Hematologic response		Cytogenetic response		Major molecular response[A] (%)	PFS	TTF
			CHR (%)	MaHR (%)	MCyR (%)	CCyR (%)			
Randomized controlled trials									
Kantarjian, 2007 (24)	D 70 mg bid	101	93	NR	**36[B]**	22[B]	16	15 mos: 93%	Mdn: NYR
	I 400 mg bid	49	82 p=0.034	NR	**29[B] p=0.4025**	8[B] p=0.041	4 p=0.038	15 mos: 54% HR 0.14 (95% CI 0.05-0.40) p<0.0001	Mdn: 3.5 mos HR 0.16 (95% CI 0.10-0.26 p<0.0001)
Randomized dose-finding trials									
Shah, 2007 (25) abstract	D 50 mg bid	166	93[C]	NR	**54[C]**	**42[C]**	NR	NR	NR
	D 100 mg qd	166	90[C]		**59[C]**	**42[C]**			
	D 70 mg bid	167	87[C]		**56[C]**	**45[C]**			
	D 140 mg qd	163	88[C]		**57[C]**	**45[C]**			
Pasquini, 2007 (26) abstract	D 70 mg bid	305	31	**47**	40	28	NR	Mdn: 11.7 mos	NR
	D 140 mg qd	304	31	**48**	37	29		Mdn: 7.9 mos	
Non-comparative trials									
Mixed phases									
Quintas-Cardama, 2007 (27)	D 70 mg bid or 140 mg qd	23	43	NR	26	9	0	NR	NR
Talpaz, 2006 (28)	dose escalation	40 CP	92	92	45	35	NR	12 mos: 100%	NR
		11 AP	45	82	27	18		12 mos: 73%	
		23 MBC	35	61	35	26		12 mos: 26%	
		10 LBC[E]	70	80	80	30		12 mos: 0%	
Quintás-Cardama, 2006 (29) abstract	dose escalation	29 CP	83	NR	58	55	**24[D]**	NR	NR
		24 AP/BC	54		59	42	**0**		
Blast crisis									
Cortes, 2007 (30)	D 70 mg bid	MBC 74	**26[F]**	34[F]	31[F]	27[F]	NR	Mdn: 5.0 mos	NR
		LBC 42	**26[F]**	31[F]	50[F]	43[F]		Mdn: 2.8 mos	
Accelerated phase									
Cortes, 2006 (31) abstract	D 70 mg bid	174	43	63	37	28	NR	Mdn: NYR	NR
Chronic phase									
Hochhaus, 2007 (32)	D 70 mg bid	387 / 186	90[F]	NR	**52[F]**	39[F]	NR	8 mos: 92.4%	NR

Notes: Efficacy outcomes that appear in "**bold**" type indicate the reported primary outcome of the study, if no outcome is in "**bold**" the primary outcome was not reported; AP, accelerated phase; BC, blast crisis; bid, twice daily; CCyR, complete cytogenetic response; CHR, complete hematologic response; CI, confidence interval; CP, chronic phase; D, dasatinib; eval, evaluable; HR, hazard ratio; I, imatinib; LBC, lymphoid blast crisis; MaHR; major hematologic response (includes patients in CHR); MBC, myeloid blast crisis; MCyR, major cytogenetic response (< 35% Philadelphia chromosome-positive cells); Mdn, median; mos, months; N, number of patients; NR, not reported; NYR, not yet reached; PFS, progression-free survival; qd, once daily; rand, randomized or enrolled; ref, reference; TTF, time-to-treatment failure;

[A]Major molecular response was defined as a ≥ 3 log decrease in *BCR-ABL* from baseline.

[B]Assessed at 12 weeks.

[C]Assessed at 6 months.

[D]Major molecular response defined as *BCR-ABL/ABL* ratio <0.05.

[E]LBC or Philadelphia chromosome-positive acute lymphoblastic leukemia.

[F]Assessed at 8 months.

Hochhaus et al (32) reported a CHR rate of 90% for 186 evaluable patients out of 387 enrolled patients with chronic phase CML. Similarly, Talpaz et al (28) and Quintás-Cardama et al (29) reported 92% and 83% CHR rates for 40 and 29 chronic phase CML patients who were enrolled in two separate dose escalation trials of dasatinib. Talpaz et al (28) also reported that 92% of patients experienced a major hematological response. Qunitás-Cardama et al (29) reported a major molecular response rate of 24% (defined as a *BCR-ABL*/ABL ratio of < 0.05). In a separate trial, Quintas-Cardama et al (27) reported that no patient achieved a major molecular response (≥ 3 log decrease in *BCR-ABL* from baseline). Of note, the rates of MCyR and CCyR for patients with chronic phase CML were similar in the trials reported by Shah et al (25), Hochhaus et al (32), and Talpaz et al (28) compared to the rates of MCyR and CCyR at 15 months reported by Kantarjian et al (24). Hocchaus et al reported progression-free survival of 92.4% at eight months for 186 evaluable patients out of a total of 387 enrolled patients (32). In addition, Talpaz et al (28) reported that progression-free survival for 40 chronic phase patients was 100% at 12 months.

Hochhaus et al (32) reported separate data for 59 patients with imatinib-intolerant CML out of 186 evaluable patients. The rates of MCyR, CCyR, and CHR were 80%, 64%, and 97%, respectively. Talpaz et al (28) reported that eight of 40 patients with chronic phase CML were imatinib-intolerant. Six patients had a MCyR of whom five had a CCyR. All eight patients achieved a CHR.

Accelerated phase

Cortes et al (31) reported complete and major hematological response rates of 43% and 63% in 174 patients with accelerated phase CML who received dasatinib 70 mg BID. Major and complete cytogenetic response rates were 37% and 28%.

In a dose escalation trial, reported by Talpaz et al (28), 45% and 82% of 11 patients with accelerated phase CML experienced a complete or major hematological response, respectively. The authors reported slightly lower MCyR and CCyR rates (27% and 18%, respectively) compared to the trial reported by Cortes et al (31). Talpaz et al (28) reported that progression-free survival at 12 months was 73%. Cortes et al (31) reported that median progression-free survival for 174 patients had not yet been reached after a minimum of nine months of follow-up.

Blast crisis

Cortes et al (30) reported on 74 patients in myeloid blast crisis who received dasatinib 70 mg BID; 26% had a CHR and 34% had a major hematological response. Major and complete cytogenetic response rates were 31% and 27%. Median progression-free survival in 68 imatinib-resistant patients was 5.0 months. Six patients in myeloid blast crisis were imatinib-intolerant at enrolment. Three of those achieved an overall hematological response of whom one had a major hematological response. None experienced disease progression. The authors also reported that for 42 patients in lymphoid blast crisis, 26% had a CHR and 31% had a major hematological response. In addition, the MCyR rate was 50% and CCyR occurred in 43%. Median progression-free survival in 37 imatinib-resistant patients was 2.8 months. Five patients in lymphoid blast crisis were imatinib-intolerant at enrolment. Two of those achieved a major hematological response. None of those patients experienced disease progression.

Talpaz et al (28) reported that of 10 patients in lymphoid blast crisis, 80% had a major hematological response and 70% had a CHR. Also, 80% had a MCyR and 30% had a CCyR. The progression-free survival for those patients was 0% at 12 months. For 23 patients in myeloid blast crisis, 61% and 35% had a major or complete hematological response. Major cytogenetic responses occurred in 35% of the same patients while 26% had a CCyR. Progression-free survival for patients with myeloid blast crisis was 26% at 12 months.

Mixed phases

Pasquini et al (26) reported a CHR rate of 31% for both 305 and 304 advanced phase CML patients randomized to dasatinib 70 mg BID compared to dasatinib 140 mg QD, respectively. Major hematological responses were similar in both arms, 47% and 48%. The rates of MCyR and CCyR were similar for each arm and no statistically significant differences were reported (Table 4). Median progression-free survival was 11.7 months (70 mg BID) and 7.9 months (140 mg QD); no p-value was reported.

Of the three single-arm non-comparative trials that included patients with any phase of CML, only one did not completely separate the trial results based on phase. Quintas-Cardama et al (27) reported on a trial of dasatinib 70 mg BID or 140 mg QD in 23 patients; the CHR rate was 43%, MCyR rate was 26%, and the CCyR rate was 9%. Of note, 83% of those patients were in accelerated phase or blast crisis when they first received dasatinib. In a separate trial, Quintás-Cardama et al (29) combined the results of patients with CML in accelerated phase and blast crisis; CHR were observed in 54% of 24 patients who received escalating doses of dasatinib. In addition MCyR and CCyR were observed in 59% and 42% of patients. The authors also reported that no patient achieved a major molecular response (*BCR-ABL/ABL* ratio < 0.05).

Adverse Events

Data on adverse events can be found in Table 5. In the RCT that compared dasatinib to imatinib in chronic phase CML, the authors reported that the rates of grade III or IV neutropenia (61% vs. 39%) and thrombocytopenia (56% vs. 14%) were higher for those that received dasatinib compared to imatinib, although no p-values were reported (24). Pleural effusions, of any grade, were also more common in the dasatinib arm (17% vs. 0%; p=not reported) as were the rates of dyspnea (any grade; 21% vs. 4%; p=not reported). The rates of any grade of peripheral edema and nausea were higher in the imatinib arm whereas the rates of any grade of diarrhea, fatigue, and headache were higher in the dasatinib arm; again no p-values were reported. In the dose comparison RCT of chronic phase CML reported by Shah et al (25), significantly lower rates of grade III or IV neutropenia and thrombocytopenia were reported for the dasatinib 100 mg QD arm compared to the other three arms combined (Table 5). In addition, the rate of any grade of pleural effusion was significantly lower in the 100 mg QD arm compared to the other three arms (p=0.028). Pasquini et al (26) also observed a similar significantly lower rate of pleural effusion, any grade, for patients with advanced phase CML randomized to dasatinib 140 mg QD compared to 70 mg BID (16% vs. 23%; p=0.024). In addition, the authors reported significantly lower rates of any grade of peripheral edema (6% vs. 13%; p=0.004), pericardial effusion (<1% vs. 4%; p=0.012), and gastrointestinal bleeding (7% vs. 12%; p=0.025) for patients randomized to a once daily dose compared to twice daily doses, respectively.

Four single-arm non-comparative trials reported data on adverse events (28,30-32). Patients in chronic phase had rates of grade III or IV neutropenia that ranged from 45% to 49% (28,32), whereas patients in accelerated phase or blast crisis had rates that ranged from 76% to 96% (28,30,31). The rates of grade III or IV thrombocytopenia ranged from 35% to 47% for trials of chronic phase CML (28,32), and from 70% to 88% for trials of accelerated phase or blast crisis (28,30,31). In all four trials pleural effusion of any grade ranged from 0% to 35% and peripheral edema ranged from 10% to 27% of patients, regardless of phase. Other non-hematological adverse events of any grade that were reported consistently among all four single-arm trials and the three RCTs were diarrhea, fatigue, headache, nausea, and dyspnea (Table 5).

Table 5. Trials of dasatinib in CML: adverse events.

Author (ref)	Treatment	N (rand/ eval)	Neut % G3-4	Thromb % G3-4	% any grade (% G3-4) Pleural effusion	Peripheral edema	Diarrhea	Fatigue	Headache	Nausea	Dyspnea
Randomized controlled trials											
Kantarjian, 2007 (24)	D 70 mg bid	101	61	56	17 (4)	10 (0)	35 (2)	30 (2)	25 (2)	24 (0)	21 (4)
	I 400 mg bid	49	39	14	0	20 (0)	29 (2)	22 (4)	10 (2)	33 (0)	4 (0)
Randomized dose-finding trials											
Shah, 2007 (25) abstract	D 50 mg bid	166	43*	31*	15*	5 (0)	24 (2)	13 (0)	19 (0)	18 (<1)	15 (4)
	D 100 mg qd	166	33*	22*	7*	10 (0)	23 (<1)	20 (1)	30 (<1)	15 (<1)	10 (1)
	D 70 mg bid	167	41*	37*	16*	10 (0)	22 (4)	16 (3)	28 (3)	25 (<1)	11 (3)
	D 140 mg qd	163	42* p=0.035	39* p=0.001	11* p=0.028	6 (0)	23 (2)	18 (2)	26 (1)	18 (<1)	15 (5)
Pasquini, 2007 (26) abstract	D 70 mg bid	305	70	70	23 (6)	13 (1)	26 (3)	15 (2)	17 (2)	17 (2)	14 (4)
	D 140 mg qd	304	65	68	16 (5) p=0.024	6 (<1) p=0.004	27 (3)	16 (1)	20 (1)	21 (1)	10 (2)
Non-comparative trials											
Mixed phases											
Quintas-Cardama, 2007 (27)	D 70 mg bid or 140 mg qd	23	NR	NR	NR	NR	NR	NR	NR	NR	NR
Talpaz, 2006 (28)	dose escalation	40 CP	45	35	13 (0)	18 (0)	18 (0)	8 (2)	10 (0)	5 (0)	10 (0)
		11 AP	82	82	0	27 (0)	45 (0)	0	27 (0)	9 (0)	27 (0)
		23 MBC	96	83	35 (13)	22 (0)	22 (4)	0	4 (0)	17 (0)	9 (9)
		10 LBC[A]	80	70	20 (0)	10 (0)	20 (0)	10 (0)	0	10 (0)	10 (0)
Quintás-Cardama, 2006 (29) abstract	dose escalation	29 CP 24 AP/BC	NR	NR	NR	NR	NR	NR	NR	NR	NR
Blast crisis											
Cortes, 2007 (30)	D 70 mg bid	74 MBC	82	84	28 (14)	19 (0)	36 (8)	12 (1)	8 (0)	16 (4)	18 (7)
		42 LBC	79	88	14 (2)	12 (0)	31 (0)	29 (5)	14 (2)	24 (0)	12 (0)
Accelerated phase											
Cortes, 2006 (31) abstract	D 70 mg bid	174	76	82	25 (3)	NR	51 (8)	26 (4)	29 (1)	NR	NR
Chronic phase											
Hochhaus, 2007 (32)	D 70 mg bid	387 / 186	49	47	19 (3)	18 (0)	30 (2)	28 (1)	34 (1)	19 (1)	27 (3)

Notes: AP, accelerated phase; BC, blast crisis; bid, twice daily; CP, chronic phase; D, dasatinib; eval, evaluable; G, grade; I, imatinib; LBC, lymphoid blast crisis; MBC, myeloid blast crisis; N, number of patients; Neut, neutropenia; NR, not reported; qd, once daily; rand, randomized or enrolled; ref, reference; thromb, thrombocytopenia;
*Statistically significant difference for D 100 mg qd compared to other three arms.
[A]LBC or Philadelphia chromosome-positive acute lymphoblastic leukemia.

V. DISCUSSION

The introduction of imatinib has resulted in a remarkably high survival rate with very few serious side effects. Responses to imatinib, in the form of major or complete cytogenetic responses, are durable; in fact once responses occur, the risks of subsequent progression to accelerated phase or blast crisis decreases during subsequent years. Thus, the attainment of a complete or major cytogenetic response appears to provide an excellent assurance of long survival up to the present follow up of five years.

Yet, despite protection from progression to accelerated phase or blast crisis, cure remains elusive with *BCR-ABL* transcripts being detectable in most patients, even in those attaining CCyR, and relapse occurs on cessation of imatinib (data not shown). Currently, patients are therefore being recommended to remain on imatinib regardless of the presence of even undetectable levels of *BCR-ABL* transcripts. Encouraging adherence to therapy therefore becomes a major focus during clinical follow up.

There appears to be a divide between excellent disease control on the one hand and continued presence of the causative mutation on the other. What is happening? It would appear that molecular events leading to accelerated phase or blast crisis are occurring in the progeny of the Philadelphia-positive stem cells rather than in the stem cells themselves. Imatinib appears to eradicate the progeny, in which there is potential for progression, but cannot eradicate the stem cells that, though not having the same potential for malignant transformation, are the source of recurrence once imatinib is discontinued. Therefore, clinical data point to the period prior to the attainment of a major cytogenetic response as being when patients are most subject to progress. The ongoing international trial originating from the South West Oncology Group is a three arm study involving standard imatinib therapy, high dose imatinib therapy and dasatinib, testing whether either a different drug (dasatinib) or a faster attainment of complete cytogenetic remission (high dose imatinib) will reduce the number of patients by foreshortening this early period of vulnerability (trial protocol available at: http://clinicaltrials.gov/ct/show/NCT00070499?order=1).

In the above trial dasatinib is being tested as first line therapy but as presently licensed it is recommended only for those patients who have failed imatinib therapy, either due to resistance or intolerance. In these patients there is a high level of response to dasatinib, both in those with chronic phase and accelerated phase. The responses to dasatinib are durable and hence dasatinib should be considered to have potential to prolong the life of patients who have failed imatinib therapy.

Dasatinib was licensed by the United States Food and Drug Administration (FDA) and given Notice of Compliance (Health Protection Branch, Health Canada) at a starting dose of 70 mg BID. Subsequent research, not published but presented and with data available, showed firstly, that dose reductions from 70 mg BID in the early trials were common leading to average received daily doses of around 100 mg/day; secondly, that 100 mg QD in a prospective randomized trial provided equivalent responses and lower incidences of adverse events and; thirdly, that once daily dosing provided lower side effects than the same dose divided twice daily. Thus, although the Sprycel® Prescribing Information recommends a starting dose of 70 mg twice daily, we recommend 100 mg once daily, and this has already become standard practice.

In summary, dasatinib is a valuable addition to existing imatinib therapy and should be made available in all situations where imatinib has failed. It is likely that this therapy will prevent the need for the hazardous bone marrow transplantation procedure in patients failing imatinib, resulting in a continuing decrease in transplantation procedures being performed.

In this discussion we have not addressed care and monitoring of patients as these are in the realm of medical practice and outside the decisions of drug funding and therefore outside the scope of this advice report.

VI. ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing trials that involved dasatinib for imatinib-resistant or –intolerant CML. Two trials were closed to recruitment as of June 13, 2007. One of those trials was published in abstract form (21), and the other has not yet been published (see below). In addition, one active single arm phase II trial and two active RCTs were identified:

Protocol ID	Title and details of trial
Active trials	
CA180-043, NCT00320190	An Open-Label, Randomized Study of Dasatinib vs. High-Dose (800 mg) Imatinib in the Treatment of Subjects With Chronic Phase Chronic Myeloid Leukemia Who Have Had a Suboptimal Response After at Least 12 Months of Therapy With 400 mg Imatinib. Outcomes: major molecular response, CCyR, time-to-major molecular response and CCyR, safety. Projected accrual: 156 patients. Last updated: May 30, 2007. Accessed: June 13, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00320190?order=1.
CA180-044, NCT00362466	An Open-Label Randomized Phase III Study of Dasatinib vs. Standard-Dose (400 mg) Imatinib Mesylate in the Treatment of Subjects With Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia Who Have Had a Suboptimal Response After 3-12 Months of Therapy With 400 mg Imatinib. Outcomes: CCyR, major molecular response, time-to- and duration of CCyR and major molecular response, progression-free survival. Projected accrual: 206 patients. Last updated: May 30, 2007. Accessed: June 13, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00362466?order=1.
CA180-109, NCT00454753	Study of Dasatinib (BMS-354825) in Subjects With Chronic Myelogenous Leukemia With Accelerated or Myeloid or Lymphoid Blast Phase or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Are Resistant to or Intolerant of Imatinib Mesylate. Outcomes: assessment of toxic effects. Projected accrual: 100 patients. Last updated: June 5, 2007. Accessed: June 13, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00454753?order=1.
Closed	
CA180-033, NCT00298987	Study of Dasatinib (BMS-354825) in Subjects with Chronic Myelogenous Leukemia With Accelerated or Myeloid or Lymphoid Blast Phase or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Are Resistant to or Intolerant of Imatinib Mesylate. Outcomes: safety. Projected accrual: 400 patients. Last updated: February 7, 2007. Accessed: June 13, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00298987?order=1.
CA180-031, NCT00337454, Sakamaki, 2007 (21) abstract	A Phase I/II Study of BMS-354825 in Subjects With Imatinib Resistant or Intolerant Philadelphia Chromosome Positive Chronic Myelogenous Leukemia and Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Are Resistant or Intolerant to Treatment. Outcomes: safety and efficacy. Projected accrual: 48 patients. Last updated: April 16, 2007. Accessed: June 13, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00337454?order=1.

VII. RECOMMENDATIONS AND EVIDENCE

Recommendations

- **Dasatinib is recommended for patients with CML in chronic phase who have primary or acquired resistance to high dose imatinib (600 mg/day).**

  Key Evidence

  - One randomized controlled trial (RCT) compared dasatinib 140 mg (70 mg twice daily) to imatinib 800 mg (400 mg twice daily) in patients with chronic phase CML who were resistant to imatinib 400 – 600 mg (24).
  - With 15 months of follow up, the dasatinib arm had statistically significant higher rates of major cytogenetic response (MCyR), complete cytogenetic response (CCyR), complete hematological response (CHR), and major molecular response (24).
  - Progression-free survival was significantly higher in the dasatinib arm compared to the imatinib arm (93% versus 54%, respectively; hazard ratio [HR], 0.14, 95% confidence interval [CI], 0.05 to 0.40) (24). In addition the median time to treatment failure was significantly higher in the dasatinib arm (not yet reached versus 3.5 months; HR, 0.16, 95% CI, 0.10 to 0.26) (24).

- **Dasatinib is recommended for patients with CML that has progressed to accelerated phase or blast crisis while on imatinib.**

  Key Evidence

  - One randomized trial (26) comparing two doses of dasatinib in patients with advanced phase CML and three single arm trials (28,29,31) of dasatinib in patients with CML in accelerated phase have reported response rates of:
    - MCyR: 27% to 40%
    - CCyR: 18% to 29%
    - CHR: 31% to 45%
  - Two single arm trials (28,30) of dasatinib in patients with CML in myeloid (MBC) or lymphoid blast crisis (LBC) have reported response rates of:
    - MCyR: LBC 50% to 80%; MBC 31% to 35%
    - CCyR: LBC 30% to 43%; MBC 26% to 27%
    - CHR: LBC 26% to 70%; MBC 26% to 35%

- **Dasatinib is recommended for patients with CML in chronic phase who are intolerant to the recommended starting dose of imatinib of 400 mg/day or to those who are intolerant to a dose of 600 mg/day, required because of failure to achieve targets of therapy or who are in accelerated phase or blast crisis.**

  Key Evidence

  - Two randomized trials (25,26) that compared different doses of dasatinib and five single arm trials included patients with imatinib-intolerant CML in chronic phase (one trial) (32), accelerated phase (one trial) (31), blast crisis (one trial) (30), or any phase (three trials) (27-29).
  - Hochhaus et al (32) included 59 patients with imatinib-intolerant CML in chronic phase of a total of 186 patients with either resistance or intolerance. A MCyR was observed in 80% of patients, CCyR in 64%, and CHR in 97%. Of the 57 patients who obtained a CHR only one patient subsequently progressed. In addition, the authors reported that dasatinib well tolerated. At eight months follow-up only 16 patients out of 186 discontinued treatment as a result of

adverse events. The authors also reported that the incidences of adverse events were comparable for patients with imatinib-resistant and –intolerant chronic phase CML.

- Cortes et al (30) reported that six of 72 patients in myeloid blast crisis were imatinib-intolerant at enrolment. Three of those achieved an overall hematological response of whom one had a major hematological response. None experienced disease progression. In addition, five patients in lymphoid blast crisis were imatinib-intolerant at enrolment. Two of those achieved a major hematological response. None of those patients experienced disease progression.

➢ **The recommended starting dose of dasatinib is 100 mg once daily for patients in chronic phase and 140 mg daily for those in accelerated phase or blast crisis.**

Key Evidence

- One randomized trial (25) comparing four doses of dasatinib in patients with chronic phase CML reported no significant differences in the rates of CHR, MCyR, or CCyR. However, the dasatinib 100 mg once daily arm had significantly lower rates of grade III or IV neutropenia and thrombocytopenia as well as any grade pleural effusion compared to dasatinib doses of 50 mg twice daily, 70 mg twice daily, and 140 mg once daily.
- One randomized trial (26) comparing two dosing schedules of dasatinib (70 mg twice daily versus 140 mg once daily) in 398 patients with CML in either accelerated phase or blast crisis reported similar rates of CHR, MCyR, and CCyR. However, the dasatinib 140 mg once daily arm had significantly lower rates of any grade pleural effusions and peripheral edema.

Qualifying Statements

Failure of imatinib therapy, the indication for dasatinib therapy, is defined as one or more of the following:

1. The presence of grades III or IV non-hematological toxicity or clinical intolerance to lower grades of toxicity.
2. Failure to attain initial targets on 400 mg/day of imatinib and not subsequently responding to an increase of imatinib to 600 mg daily, targets being:
    a. Complete hematologic remission at 3 months.
    b. Any cytogenetic response at 6 months.
    c. A major cytogenetic response at 12 months.
    d. A complete cytogenetic response at 18 months.
3. Loss of previously attained targets or a significant increase in *BCR-ABL* transcripts (≥ 0.5 log from best response) (33).
4. Progression to accelerated phase or blast crisis and failing to respond to an increased dose of imatinib of at least 600 mg.

Definitions of endpoints/targets of initial therapy:

- CHR (chronic phase)
    - White blood count (WBC) ≤ upper limit of normal (ULN)
    - Platelets < 450,000/mm^3
    - No blasts or promyelocytes in peripheral blood
    - < 5% myelocytes plus metamyelocytes in peripheral blood
    - Basophils in peripheral blood < 20%
    - No extramedullary involvement (including no hepatomegaly or splenomegaly)

- CHR (accelerated phase/blast crisis)
  - WBC < ULN
  - Absolute neutrophil count (ANC) ≥ 1000/mm^3
  - Platelets ≥ 100,000/mm^3
  - No blasts or promyelocytes in peripheral blood
  - Bone marrow blasts ≤ 5%
  - < 5% myelocytes plus metamyelocytes in peripheral blood
  - Basophils in peripheral blood < 20%
  - No extramedullary involvement (including no hepatomegaly or splenomegaly)

- CCyR
  - 0% Ph-positive cells in metaphase in bone marrow

- Partial cytogenetic response (PCyR)
  - 1% to 35% Ph-positive cells in metaphase in bone marrow

- MCyR
  - CCyR + PCyR
  - ≤ 35% Ph-positive cells in metaphase in bone marrow

- Major molecular response (MMoR)
  - ≥ 3 log suppression of *BCR-ABL* transcripts from baseline

- Complete molecular response (CMoR)
  - Undetectable levels of *BCR-ABL transcripts* (usually ≥ 4 – 4.5 log suppression from baseline.

Related Guidelines

Practice Guideline #6-15: Treatment of Chronic Myeloid Leukemia with Imatinib.

VIII. CONFLICTS OF INTEREST

The authors of this report declared that there were no potential conflicts of interest related to the topic of this CED-CCO advice report.

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Contact Information
Dr. K. Imrie, Co-Chair, Hematology Disease Site Group
Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5
Phone: 416-480-4757 Fax: 416-480-6002
or
Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group
Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2
Phone: 905-387-9711 ext. 62484 Fax: 905-575-6340

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Appendix 1. Literature search strategies.

MEDLINE (OVID), MEDLINE Daily Update (OVID), and MEDLINE In-Process & Other Non-Indexed Citations (OVID)

1. exp leukemia, myeloid, chronic/
2. leukemia, myeloid/
3. exp leukemia, myeloid, philadelphia-positive/
4. chronic myel: leuk?emia.mp.
5. cml.mp.
6. or/1-5
7. dasatinib.mp.
8. bms354825.mp.
9. bms 354825.mp.
10. Sprycel.mp.
11. or/7-10
12. 6 and 11
13. limit 12 to (humans* and English language)

*The limit "humans" cannot be used in MEDLINE Daily Update or MEDLINE In-Process & Other Non-Indexed Citations.

EMBASE (OVID)

1. leukemia/
2. myeloid leukemia/
3. chronic myeloid leukemia/
4. chronic leukemia/
5. Philadelphia 1 chromosome/
6. chronic myel: leuk?emia.mp.
7. cml.mp.
8. or/1-7
9. "N (2 Chloro 6 Methylphenyl) 2 [6 [4 (2 Hydroxyethyl) 1 Piperazinyl] 2 Methyl 4 Pyrimidinylamino] 5 Thiazolecarboxamide"/
10. dasatinib.mp.
11. bms354825.mp.
12. bms 354825.mp.
13. Sprycel.mp.
14. or/9-13
15. 8 and 14
16. limit 15 to (human and English language)

Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), and the Database of Abstracts of Reviews of Effects (DARE)

1. dasatinib.mp.
2. Sprycel.mp.
3. bms354825.mp.
4. bms 354825.mp.
5. or/1-4**

**No search results were produced for any of these terms.

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Search terms used: dasatinib, Sprycel, BMS 354825.

Appendix 2. Definitions of efficacy outcomes reported in each trial.

Outcome	Definition	Kantarjian, 2007 (24)	Shah, 2007 (25) abstract	Hochhaus, 2007 (32)	Talpaz, 2007 (28)	Cortes, 2006 (31) abstract	Cortes, 2007 (30)	Pasquini, 2007 (26) abstract	Quintas-Cardama, 2007 (27)	Quintás-Cardama, 2006 (29) abstract
CHR CP-CML	1) WBC ≤ ULN 2) platelets < 450,000/mm^3 3) no blasts or promyelocytes in peripheral blood 4) < 5% myelocytes plus metamyelocytes in peripheral blood 5) basophils in peripheral blood < 20% 6) no extramedullary involvement (including no hepatomegaly or splenomegaly)	**X**	**NR**	**X[A]**	**X**	**NA**	**NA**	**NA**	**NR**	**NR**
CHR AP/BC-CML	1) WBC ≤ ULN 2) ANC ≥ 1000/mm^3 3) platelets ≥ 100,000/mm^3 4) no blasts or promyelocytes in peripheral blood 5) bone marrow blasts ≤ 5% 6) < 5% myelocytes plus metamyelocytes in peripheral blood 7) basophils in peripheral blood < 20% 8) no extramedullary involvement (including no hepatolomegaly or splenomegaly)	**NA**	**NA**	**NA**	**X**	**NR**	**X[A]**	**NR**	**NR**	**NR**
MaHR AP/BC-CML	CHR ***or*** NEL NEL: 1) same as CHR ***except***: 2) 20,000/mm^3 ≤ platelets < 100,000/mm^3 ***OR*** 3) 500/mm^3 ≤ ANC < 1000/mm^3	**NA**	**NA**	**NA**	**X**	**NR**	**X**	**NR**	**NR**	**NR**
CCyR	0% Ph-positive cells in metaphase in bone marrow	**X**	**NR**	**X**	**X**	**NR**	**X**	**NR**	**NR**	**NR**
PCyR	1% to 35% Ph-positive cells in metaphase in bone marrow	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
MCyR	CCyR + PCyR; ≤ 35% Ph-positive cells in metaphase in bone marrow	**X**	**NR**	**X**	**X**	**NR**	**X**	**NR**	**NR**	**NR**
TTF	Time from randomization to progression or end of treatment (lack of response, study drug intolerance, or off-treatment for any reason)	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**

Notes: ANC, absolute neutrophil count; AP/BC-CML, accelerated phase/blast crisis chronic myeloid leukemia; CCyR, complete cytogenetic response; CHR, complete hematological response; CP-CML, chronic phase chronic myeloid leukemia; MCyR, major cytogenetic response; NA, not applicable either due to, 1) the study did not include patients with this phase of CML or, 2) authors did not report on this outcome; NEL, no evidence of leukemia; PCyR, partial cytogenetic response; Ph, Philadelphia chromosome; TTF, time-to-treatment failure; ULN, upper limit of normal; WBC, white blood cell count; X, indicates that a trial reported the definition of that specific outcome variable.

[A]Basphils is peripheral blood < 2%.