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Chronic Myeloid Leukemia

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Background

Chronic myelogenous leukemia (CML) is a disease characterized by the expression of *BCR-ABL*, an oncogenic tyrosine kinase that induces bone marrow stem cell proliferation. Untreated, there is progression from a relatively benign chronic phase, lasting 3 to 5 years, to a rapidly fatal acute leukemia (blast crisis). Impressive therapeutic advances in the management of CML have occurred in the past three decades, starting with the introduction of the tyrosine kinase inhibitor (TKI) imatinib, which dramatically improved survival in a large proportion of patients, and then introduction of second and third generation TKIs namely nilotinib, dasatinib, bosutinib and ponatinib for patients with imatinib resistance or intolerance. Finally, there has recently been the introduction of Asciminib, which acts by a novel mechanism. Nilotinib and Dasatinib are approved in Alberta along-side Imatinib as first-line agents for patients newly diagnosed with CML. Bosutinib is approved for second line therapy, Asciminib in third line or beyond while Ponatinib is available in special circumstances. Allogeneic hematopoietic stem cell transplantation remains available for selected patients with CML but is rarely utilized. CML patients treated with TKI therapy have now been shown to have a near normal life expectancy.

Guideline Questions

1. What diagnostic and baseline investigations are recommended for adult patients with suspected or confirmed CML?
2. What are the recommended treatment options for CML?
3. What are the criteria for monitoring response to treatment?
4. When is it appropriate to consider stopping TKI therapy for CML?

Search Strategy

In 2012, the recommendations developed by the Canadian Consensus Group on the Management of Chronic Myelogenous Leukemia were converted to an Alberta guideline, based closely on the European Leukemia Net Guidelines current at the time. [1,2]. In addition, guidelines developed by Cancer Care Ontario (CCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence (NICE) were reviewed in the process of developing this document.

The 2015, 2017, 2020 and 2023 updates incorporated new evidence from research involving in the management of CML.

Target Population

The following guidelines apply to adults over 18 years of age. Different principles apply to pediatric patients.

Recommendations

Diagnosis and Prognosis:

1. The classification of CML is according to the definitions set out by the World Health Organization (WHO.
2. The Sokal, Hasford and/or ETLS scores should be calculated at diagnosis to aid in prognostication.
3. The various scores have been developed for clinical trial use in chronic phase patients. In practice, the 10% reduction in bcr-abl1 quantification at 3 months is the best indicator of a good response to TKI therapy

Diagnosis and Baseline Investigations:

4. The following investigations are recommended at diagnosis for all patients with suspected or confirmed CML:

- CBC and differential
- Bone marrow aspirate and biopsy
- Baseline bone marrow cytogenetics
- Peripheral blood or bone marrow nested PCR to determine the involved transcript type.
- Liver function tests, lipase, glucose, urate, creatinine, lipid panel, fasting glucose, HgbA1c, lipid panel

Treatment Options:

5. Treatment with a TKI as first-line treatment for all newly diagnosed CP-CML patients is recommended. Currently in Alberta therapy is begun with imatinib, dasatinib or nilotinib. The choice of TKI should be guided by an individual patient's comorbidities. Patients having achieved their therapeutic milestones with and tolerant of a TKI should continue on it. Hydroxyurea is useful in controlling leukocytosis and thrombocytosis while waiting for results of BCR/ABL test results. Allopurinol should be administered for prevention of hyperuricemia complications.

A second-generation TKI (nilotinib, dasatinib or bosutinib) is recommended for patients with imatinib resistance/ intolerance, or who fail to achieve any of the treatment milestones while on imatinib. In case of resistance to a front-line second generation TKI mutation analysis and HLA typing of the patient and siblings should be sent. The choice of a second line TKI should be guided by an individual patient's comorbidities. The presence of specific mutations will override other considerations when determining the optimal agent to employ. Asciminbi, a novel STAMP inhibitor, is available for third line therapy. Finally, the third-generation TKI, ponatinib, is available in patients for whom other therapy is not appropriate, including CML that isT315I mutation positive or when there is resistance or intolerance to all other CML directed therapy.

6. Patients presenting with accelerated phase disease should be started on a TKI with early consideration given to transplantation

7. Patients presenting with blast phase disease should be treated with induction type chemotherapy along with a TKI and early consideration should be given to transplantation.
8. Allogeneic stem cell transplant (SCT) remains a treatment option as it is the only known cure; this option may be selected at any point during the treatment course based on informed patient preference. Allogeneic SCT is the preferred option in patients with evidence of clonal progression or with advanced-phase disease. The most effective treatment available should be employed while awaiting transplantation.
9. All transplant-eligible patients who fail second-line TKI therapy due to resistance should be evaluated for transplantation. Transplantation should be considered in patients with evidence of clonal progression by bone marrow cytogenetics or next generation sequencing.
10. Interferon-α (IFNα) should be considered only in patients who are unable to tolerate a TKI and are ineligible for SCT or entry in a clinical trial, or in women who wish to become pregnant. Treatment should be employed with the guidance of a physician with clinical experience using IFNα.

Monitoring Treatment Response:

11. Peripheral blood Q-RT-PCR should be performed every 3 months. If a molecular response greater than 4.5-log reduction (MMR] is reached and stable for 2 years, the frequency of Q-RT-PCR may in a compliant patient may be reduced in an individualized fashion. Bone marrow karyotyping may be performed at 1 year to confirm CCyR and to detect clonal progression or other abnormalities. Thereafter, marrow karyotyping should not be performed annually unless there are clonal abnormalities that need to be followed.
12. The recommended definition of first-line optimal treatment response to tyrosine kinase inhibitors (TKIs) in accordance with European Leukemia Net guidelines, are defined as:

- BCR-ABL1 ≤10% (at least a 1-log reduction) at 3 months
- BCR-ABL1 <1% (2-log reduction) at 6 months
- BCR-ABL1 ≤0.1%(≥3-log reduction) at 12 months, and thereafter

13. The recommended definition of treatment failure on first-line TKIs in accordance with European Leukemia Net guidelines, are defined as:

- Non-CHR and/or BCR-ABL > 10% if confirmed within 1-3 months
- BCR-ABL1 >10%
- BCR-ABL1 >1%
- Thereafter, loss of CHR, confirmed loss of CCA/Ph+ or MMR (on two consecutive tests of which BCR-ABL1 transcripts level rise by ≥1% in at least 1 test)

14. Compliance to TKI prescription should be assessed at every visit, particularly in those patients with a suboptimal response
15. BCR-ABL Kd mutation testing is recommended in patients who fail to achieve treatment milestones, or if there is a loss of response. Mutational analysis should always be performed before switching TKIs.

16. Human leukocyte antigen (HLA) typing of the patient and sibling should be considered when a transplant appropriate patient presents in AP or BC or when there is suboptimal response, loss of a previously obtained response or significant intolerance.
17. Repeat cytogenetic and mutation testing after treatment with a second-line TKI are advised if no improvement in therapeutic milestones or a loss of response is observed.
18. Second-line optimal treatment response criteria, in accordance with European Leukemia Net guidelines, are the same as with front-line therapy
19. Second-line treatment failure criteria, in accordance with European Leukemia Net guidelines, are the same as with front line therapy
20. Cardio-vascular risk factors should be optimized in all patients on TKI therapy given their side effect profiles. HgbA1c and lipid panels should be monitored yearly.
21. In patients who have achieved a stable major molecular remission dose reduction may be considered in order to improve symptom burden.
22. Discontinuation of TKI therapy may be considered in patients who have been on treatment for at least 5 years with a QPCR >4.5 for at least 2 consecutive years. Upon discontinuation QPCR should be monitored every month for one year. If the log reduction lowers by 0.5 log for 2 consecutive months or by 1 log at any interval, TKI therapy should be reinstituted. We suggest resuming the original TKI therapy that was used in order to achieve maximal MMR prior to attempting a treatment free remission (TFR).
23. Men can continue TKI therapy for conception. Women should discontinue TKI's prior to conception or as soon as pregnancy is confirmed. Interferon-α should be substituted if the disease is not well controlled or progresses.

Discussion

I. Diagnosis

Staging of CML is according to the definitions set out by the WHO [3].

- ***Chronic phase (CP):*** peripheral blood blasts fewer than 10% in the blood and bone marrow and absence of accelerated phase features
- ***Accelerated phase (AP): (One or more of the following)***
  - *Persistent or increasing WBC (>10x10^9/L), unresponsive to therapy*
  - *Persistent or increasing splenomegaly, unresponsive to therapy*
  - *Persistent thrombocytosis (>1000x10^9/L), unresponsive to therapy*
  - *Persistent thrombocytopenia (<100x10^9/L) unrelated to therapy*
  - *20% or more basophils in the PB*
  - *10-19% blasts in the PB and/or BM*

- *Additional clonal chromosomal or molecular abnormalities in Ph^+ cells at diagnosis that include 'major route' abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2*
- *Any new clonal chromosomal abnormality in Ph^+ cells that occurs during therapy*

- ***Blast crisis (BC) phase:*** blasts ≥ 20% of peripheral blood white blood cells or nucleated bone marrow cells, extramedullary blast proliferation, and large foci or clusters of blasts on bone marrow biopsy.

II. Prognosis

The Sokal, Hasford and/or ETLS score should be calculated in newly diagnosed patients with CML; there is no evidence to support the use of one method over another. The Sokal score was the first scale to calculate CML risk level.[4] A 2009 study demonstrated that the Sokal score was correlated with cytogenetic and molecular responses in imatinib-treated patients.[5]

For patients receiving IFNα therapy, the Hasford prognostic score remains the most reliable prognostic tool.[6] Sokal and Hasford scores can be calculated here.

The EUTOS score, based on spleen size and percent basophils in peripheral blood, can be used to predict CCyR at 18 months after starting treatment with a TKI .[7] The EUTOS score can be calculated here. The Hammersmith prognostic scoring system, which has been developed for patients receiving imatinib following failure with IFNα is noteworthy, [8] but is not a widely employed method and has not been validated in patients receiving a front-line TKI.

The ETLS score is based on an analysis of 2290 patients with chronic phase CML treated with imatinib in six clinical trials, and further validated in an independent sample of 1120 patients. In both sets of patients, the ETLS score was better able to predict the probability of dying from CML compared to Sokal, Euro and the EUTOS score. The ETLS score identified 61% of patients as low risk, and 12% of patients as high risk. The probability of dying from CML (8-year probability) was 7% (95%CI: 5-10%) in the high-risk group, 4% (95%CI 3-6%) in the intermediate risk group and 3% (95%CI: 2-4%) in the low risk group. The study found that higher age, more peripheral blasts, bigger spleen and low platelet counts were significantly associated with increased probabilities of dying of CML.[9] An online calculator for the ETLS score is available here.

Baseline characteristics such as age, spleen size, platelet count, peripheral blood % counts, basophil count, and eosinophil count should be recorded so that alternative scores can be calculated at a later time.

The introduction of TKIs for the treatment of CML has dramatically improved overall survival among CML patients. A study of 2,662 patients with CML from Sweden (diagnosed between 1973 and 2013) demonstrated significant improvements in life expectancy among CML patients over the study period, particularly among younger patients. Patients diagnosed in 2013, on average, lose <3 life-years as a

result of their CML diagnosis.[10] Taken together, TKIs along with allogeneic stem cell transplantation and other factors have contributed to the life expectancy in patients with CML approaching that of the general population today.

III. Diagnosis and Baseline Investigations

The following investigations are recommended at diagnosis for all patients with suspected or confirmed CML:

- Bone marrow aspirate and biopsy
- Baseline bone marrow cytogenetics
- Peripheral blood or bone marrow nested polymerase chain reaction (PCR)

The bone marrow aspirate and biopsy are helpful in quantifying blasts, and other morphological findings may support a diagnosis of advanced-phase CML.

The *BCR-ABL1* gene and its resulting transcripts provide specific markers for the diagnosis and monitoring of minimal residual disease (MRD). Methods available to detect the *BCR-ABL1* gene include conventional cytogenetics (karyotype analysis), fluorescence in situ hybridization (FISH), and nested PCR.

Bone marrow karyotype analysis is the only method that allows for the evaluation of all chromosomes and is recommended at diagnosis to identify the presence of additional cytogenetic abnormalities. Karyotyping is also useful in the context of primary and secondary resistance to evaluate the possibility of clonal evolution, and when a responding patient has abnormal blood counts. Repeat karyotyping should be done in the setting of not meeting therapeutic milestones, loss of a previous response or newly abnormal blood counts.

FISH lacks the sensitivity necessary for monitoring MRD. Data have shown that the deletion on the derivative 9 is not prognostic for patients on imatinib. Thus, FISH is no longer necessary to document the presence of this deletion.

Q-RT-PCR enables the detection and accurate quantitation of *BCR-ABL* transcript levels, and is now widely used for the detection and quantification of MRD [11]. Two kinds of fusion transcripts, resulting from major (e14a2, e13a2) and minor (e1a2) breakpoints, can be distinguished according to the breakpoint within the *BCR* region. These transcripts encode the p210 (e14a2, e13a2) and p190 (e1a2) fusion proteins, the transcripts of which can be detected using Q-RT-PCR techniques.

All patients should have liver function tests, lipase, glucose, urate, cholesterol, fasting glucose, HgbA1c, lipid panel to assess for possible comorbidities, and as a baseline for possible expected complications.

Ratios and Log Reduction

Due to RNA degradation over time, the analysis of an internal control gene is mandatory to obtain reliable transcript results. Several control genes are used in different laboratories (e.g. *BCR*, *ABL1* or *G6PDH*). Results can be reported as the ratio between *BCR-ABL1* and the control gene or log reduction in level of transcripts from diagnostic values. The two molecular laboratories in Alberta use ABL1 as their control gene. To calculate the log reduction, one must have a diagnostic ratio for the patient in question, or a calculated laboratory diagnostic median ratio. Either of these can be used as the baseline, but using a laboratory median is strongly recommended; this is derived from calculating the median transcript ratio from 30 to 50 patients at diagnosis. The log reduction using the median ratio is calculated using Log (Baseline Median Ratio/Current Ratio) = log reduction. Patients who achieve at least a 3-log reduction in *BCR-ABL1* transcripts within 12 to 18 months after initial treatment are defined as having achieved a MMR and to have a low probability of disease progression [12,13]. Increasing levels of *BCR-ABL1* transcripts are predictive of loss of response if levels rise more than 0.5 log over two serial samples [13,14]. At levels below 3 logs, increasing transcripts must be confirmed as there is variability in the assay at low transcript levels.

International Scale (IS)

The International Scale allows transcript levels to be reported as a percentage, with 100% being baseline for newly diagnosed patients and 0.1% being equivalent to a 3-log reduction. To normalize a laboratory ratio, a conversion factor is determined so that the baseline ratio between *BCR-ABL1*/*CONTROL GENE* is equivalent to 100% [14].

International Standardization

When obtaining a conversion factor, a further level of standardization is recommended by normalizing results against those from a reference laboratory with values calibrated against the initial IRIS trial data. This last standardization allows laboratories to have a similar way of reporting results (IS), and ensures the ratio reported for patients corresponds to data obtained in clinical trials [14-17]. All reporting should be done using international standardization.

IV. Treatment Options

Chronic-phase CML

Tyrosine kinase inhibitors (TKI's) are the first-line treatment for all newly diagnosed chronic phase-CML patients. The recommended starting doses are:

- Imatinib: 400 mg/day
- Nilotinib: 300 mg twice daily
- Dasatinib: 100 mg/day
- Bosutinib 300 mg/day (not approved for front line therapy in Alberta)

All TKIs should be used with caution in any patient with a history of cardiovascular disease or peripheral vascular disease. The choice of the TKI is guided by an individual patient's comorbidities and ability to comply with the dosing regimen. Table 1 presents comorbidities predicting adverse events during treatment with standard TKI's. Compliance with TKI therapy is of the utmost importance. It has been shown to decrease over time and impact outcome [18-20] and thus should be assessed diligently at each visit.

Table 1. Comorbidities predicting adverse events during TKI treatment (adapted from Mederios, 2018) [21]

TKI	Cardiovascular, Pulmonary, and Metabolic Toxicities	Careful Monitoring and Caution Advised for Certain Patients
Imatinib	-CHF and left ventricular dysfunction -Rare pulmonary toxicity	-Patients with cardiac disease -Patients with risk factors for cardiac failure
Dasatinib	-PAH, pleural effusions, pneumonitis -QT prolongation	-Patients with preexisting cardiopulmonary disease -Patients who may develop QT prolongation
Nilotinib	-QT prolongation (black-box warning) -Cardiac and arterial vascular occlusive events -Hyperlipidemia or hyperglycemia -Sudden deaths have been reported in CP patients with imatinib-resistant/intolerant CML with a history of cardiac disease or significant cardiac risk factors -Rare pleural effusions	-Patients at risk for hyperlipidemia or hyperglycemia -Avoid in patients with long QT syndrome -Avoid in patients with hypokalemia or hypomagnesemia
Bosutinib	-Cardiovascular, pulmonary, and metabolic toxicities are generally low -Rare pleural effusions	-Patients with cardiovascular risk factors
Ponatinib	-Vascular occlusion (black-box warning) -Heart failure (black-box warning) -Hypertension -Arrhythmias -Possible pulmonary hypertension	-Patients with hypertension -Patients at risk for arrhythmias -Patients at risk for heart failure -Patients with preexisting cardiopulmonary disease

Imatinib Mesylate.

The utility of imatinib as first-line therapy for CML was established by the IRIS trial, a phase III study that randomized 1,106 newly diagnosed CP-CML patients to imatinib 400 mg/day or IFNα plus cytarabine [22]. At six-year follow-up, the cumulative best CCyR rate was 82%; 63% of patients randomized to imatinib and still on treatment showed CCyR at last assessment [23]. During the sixth year of treatment, there were no reports of disease progression to AP- or BC-CML. The toxicity profile was unchanged. The estimated overall survival was 88%; CML-specific survival was 95%. The IRIS study has been further updated now with median 10.9 years of follow-up. The 10-year overall survival rate is reported at 83.3% in those patients randomized to the imatinib arm (cross-overs not included). Approximately half of the patients assigned to the imatinib arm completed study treatment with

imatinib, and 82.8% had a complete cytogenetic response. Imatinib-related adverse events were uncommon and typically occurred within the first year of treatment[24].

A higher starting dose of imatinib (600-800 mg/day) has been proposed based on a retrospective analysis of the IRIS dataset [25], and the observation that a more rapid treatment response is associated with a lower risk of progression and better patient outcomes [26,27]. In the Rationale RIGHT trial, the proportion of patients receiving initial treatment with imatinib 400 mg BID that achieved MMR was 48% at six months and 63% at 18 months [28]. Superior responses with a starting dose of imatinib 600-800 mg/day were also reported in the TIDEL I trial, the phase III TOPS trial, and the GIMEMA CML working party phase II study [29-31]. No benefit was seen with high-dose imatinib in a LeukemiaNet study of high Sokal risk patients [32]. A meta-analysis of four trials (n=1,673) comparing higher-dose imatinib (≥600 mg/day) with standard dosing (400 mg/day) found modest improvements in the rates of CCyR (risk ratio [RR] 1.17) and MMR (RR 1.26) at 12 months, but no difference in all-cause mortality or disease progression [33]. An expert review found that high-dose imatinib could induce a sustained response in patients with cytogenetic failure or acquired resistance but was less effective in patients with a suboptimal molecular response [34]. It has not been determined if the improved rates of CCyR and MMR will translate to better long-term outcomes. Adverse events requiring treatment discontinuation occur more commonly with higher-dose imatinib and may adversely affect adherence to this regimen. Current National Comprehensive Cancer Network guidelines consider high-dose front-line imatinib to have only a limited role at this time [35]. This is therefore not recommended in Alberta.

Nilotinib.

Nilotinib is a selective TKI that is about 30-fold more potent than imatinib [36]. Its efficacy as a first-line therapy in CP-CML was demonstrated in the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) trial [37]. At 12 months, the MMR rate was 44% with nilotinib 300 mg BID, 43% with nilotinib 400 mg BID and 22% with imatinib 400 mg/day. CCyR rates at 12 months were also higher with the two nilotinib doses (80%, 78%) compared to imatinib (65%). Progression to AP- or BC-CML was <1% with nilotinib versus 4% with imatinib. At 24-month follow-up, MMR rates with nilotinib were 71% and 67% versus 44% with imatinib [38]. Rates of progression to AP- or BC-CML (including clonal evolution) were significantly lower with nilotinib compared to imatinib (0.7% and 2.7% vs. 6.8%). Additional supportive data on the use of first-line nilotinib were obtained in two phase II studies [39,40]. In 2011, Health Canada approved nilotinib 300 mg BID as a first-line treatment option for CP-CML. Retrospective studies [41-44] and a prospective study [45] have found higher rates of peripheral artery occlusive disease among patients with CML receiving nilotinib compared to patients receiving imatinib. The prospective study included patients currently enrolled on the ENESTnd trial. Of the total cohort (n=159), 54 patients were on first-line imatinib, 33 were on first-line nilotinib, 33 had previous imatinib exposure and were on second-line nilotinib, 25 had previous nilotinib and were on another therapy, and 14 were nilotinib-nave patients not receiving imatinib. Peripheral artery occlusive disease was reported in 5 patients, all of which were in the first-line, second-line, or post-nilotinib groups (Kim et al. 2013). Similarly, retrospective data has indicated that

peripheral artery occlusive disease occurs in approximately 2.1-12.5 % of CML patients receiving nilotinib [41-45].

Dasatinib.

Dasatinib is a Src/Abl TKI with activity against a range of imatinib-resistant mutations. It is about 325-fold more potent than imatinib [46]. Efficacy in the first-line setting was demonstrated in the phase III DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients) trial [47]. At 12 months, the rate of confirmed CCyR was 77% with dasatinib 100 mg/day compared to 66% with imatinib 400 mg/day; MMR rates were 46% versus 28%, respectively. Rates of progression to AP- or BC-CML were not significantly different with dasatinib versus imatinib (2.0% vs. 3.5%). At 24 months, CCyR rates were 86% and 82% with dasatinib and imatinib, respectively [48]. MMR rates were significantly higher with dasatinib (64% vs. 46%), with 17% versus 8% achieving a 4.5-log reduction. At three years, MMR, MR^4, and $MR^{4.5}$ were significantly better in the dasatinib arm ($p < 0.001$, $p=0.0064$, $p<0.001$, respectively); however, at three years, progression free and overall survival were not significantly higher in the dasatinib arm (Jabbour et al. 2014). Two phase II trials provide supportive evidence of the efficacy of dasatinib in the front-line setting [49,50]. The phase II randomized study NordCML006 (n=46) compared first-line dasatinib (100mg QD) vs imatinib (400mg QD) and showed higher MR(3.0) in the dasatinib group at 3 months (36% vs 8%; $p=0.02$) and 12 months (81% vs 46%; $p=0.02$), but this improvement did not remain significant at 18 months (73% vs 65%; $p>0.05$) [51]. A trial of 246 previously untreated chronic-phase-CML patients randomized patients to receive dasatinib 100 mg or imatinib 400 mg. The percentage of patients achieving complete cytogenetic response was significantly higher in the dasatinib group (84%) compared to the imatinib group (69%) ($p=0.040$). Overall, progression free, and relapse free survival were higher in the dasatinib arm, though not significantly. A larger proportion of dasatinib patients (58%) experienced grade 3-4 toxicities compared to the imatinib group (35%) ($p<0.001$). Thrombocytopenia, and pleural effusion were more common in the dasatinib arm, whereas edema, nausea and muscle pain were more common in the imatinib arm [50].

A study which pooled 2705 patients who were enrolled in clinical trials receiving a combined 5890 patient years of dasatinib exposure found peripheral arterial occlusive disease (PAOD) (n=1) and PAOD-related events (n=5) in 0.2% of patients all of which were grade ≤3 (le Coutre et al. 2013). Multiple studies evaluating second-line dasatinib have found high rates of pleural effusion, skin rash, and diarrhea (in >15% of CML patients) and increase in NK cells and peripheral edema (in 4-15% of CML patients). Pulmonary hypertension, pericardial effusion, viral reactivation, and major bleeding were reported in 1-4% of CML patients [52-56]. Dasatinib 100 mg/day was approved as a first-line treatment option for CP-CML by Health Canada in 2011.

Bosutinib.

The randomized phase III trial BELA randomly assigned 502 patients to bosutinib (500mg/day) or imatinib (400mg/day). The complete cytogenetic response rate at 12 months was not significantly different between bosutinib and imatinib ($p=0.601$) (primary end point). However, the major molecular

response at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) compared with imatinib (27%; 95% CI, 22% to 33%; two-sided P < .001) [57]. Time to CCyr and MMR was faster with bosutinib compared to imatinib (p<0.001) and on-treatment transformation to accelerated/blast phase occurred more frequently on imatinib (4%) compared to bosutinib (2%). In this trial 3 CML-related deaths occurred in the bosutinib arm compared with 8 in the imatinib arm. Safety profiles were distinct; GI and liver-related events were more frequent with bosutinib, whereas neutropenia, musculoskeletal disorders, and edema were more frequent with imatinib [57].

In the BFORE trial[58] 536 patients with newly diagnosed chronic-phase CML were randomized 1:1 to bosutinib (400mg/d) vs imatinib (40mg/d). At 12 months the MMR rate was significantly higher in the bosutinib group (47.2% vs 36.9%) as was the CCyR (77.2% vs 66.4%). 4 patients receiving bosutinib and 6 patients receiving imatinib experienced disease progression to accelerated or blast phase. Grade 3 or greater diarrhea and increased ALT and AST levels were more common with bosutinib. Cardiac and vascular toxicities were uncommon.

Anecdotal evidence suggested that the diarrhea experienced with bosutinib can be mitigated with a slow ramp up of dosing upon initiation. Bosutinib is not currently approved in front line therapy in Alberta.

Accelerated-Phase and Blast-Crisis CML

Phase II trials have investigated the efficacy of front-line imatinib 400-800 mg/day in AP-CML [66-69] and BC-CML [70,71]. In AP-CML, the GIMEMA CML Working Party reported a cumulative best rate of a major cytogenetic response (MCyR) was 30% with imatinib 600 mg/day; progression-free survival (PFS) at 7-year follow-up was 36.5% [66]. In the STI571- 0109 phase II trial, 24% achieved MCyR with imatinib 400-600 mg/day; 12-month PFS was 59% [67]. At 48 months, the estimated overall survival rate was 45% for patients receiving imatinib 600 mg/day; however, 82% had discontinued treatment, primarily due to progression or lack of efficacy [68].A recent comparison of imatinib and allogeneic SCT in AP-CML reported 6-year PFS >80% with both approaches in low-risk patients; however, SCT was superior to imatinib in intermediate-risk (6-year PFS 92.9% vs. 55.7%) and high-risk patients (5-year PFS 100% vs. 18.8%) [69]. A phase II trial of nilotinib 400 mg BID in AP-CML with imatinib resistance/intolerance reported an MCyR rate of 32%, with 66% maintaining MCyR at two years [42]. In the phase II START-A trial of dasatinib 70 mg BID in AP-CML, the MCyR and CCyR rates were 39% and 32%, respectively; 12-month PFS was 66% [72].

In the phase II GIMEMA trial in BC-CML, 50% of patients returned to CP-CML and 17% had a cytogenetic response with imatinib 600 mg/day, although long-term outcomes were not significantly affected [70]. Median survival was 7 months. In the STI571- 0102 phase II trial, 16% had MCyR with imatinib 400-600 mg/day; median survival was 6.9 months [71]. At 48 months, 97% had discontinued imatinib, largely due to progression or lack of efficacy [68]. Second-generation TKIs have also demonstrated activity in BC-CML. In a phase III trial of dasatinib 70 mg BID or 140 mg OD, 25-28% of

BC-CML patients achieved MCyR [73]. Supportive data were obtained in a phase II trial [74]. Data for nilotinib are more limited, although a phase II trial has reported marrow responses or a return to CP in about one-quarter of BC-CML patients [75]. Thus, TKIs can induce a sustained response and provide a survival advantage over previous therapies. However, there is a need for improved treatment approaches for patients in advanced phases of CML. Table 2 presents recommended doses of TKI in AP- and BC-CML.

Table 2. Recommended TKI doses in AP- and BC-CML

	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Accelerated phase	600 mg daily	400 mg BID	70 mg BID	500 mg OD	45 mg OD
Blast crisis	800 mg daily	--	70 mg BID	500 mg OD	45 mg OD

V. Special topics

Treatment of Elderly Patients with CML

The introduction of TKIs for the initial treatment of CML has dramatically improved overall survival of younger CML patients. However, the utility of TKIs in the elderly remains somewhat unclear as several retrospective studies have been unable to demonstrate relative survival benefit, while other show dramatic improvements.

A study analysing 5138 patients diagnosed with CML before and after the introduction of TKIs using the Surveillance, Epidemiology, and End Results (SEER) database showed that overall survival in 65-74-year-olds increased from 38% to 51%- and 75-84-year olds increased from 19% to 36% [59]. Another study using the SEER database to identify 423 CML patients showed that 75% of patients aged 60-79 years and 46% of patients aged ≥80 years were treated with imatinib, and those who received imatinib survived significantly longer than those who did not with no differences in race/ethnicity, socioeconomic status, urban/rural residence, comorbidities, or insurance status between imatinib users and non-users [60]. Another study, again using the SEER database, examining 11,880 CML patients, showed 5-year relative survival advantage of age ≥75 years CML patients who were treated with TKIs (including second-generation TKIs) compared to those who did not [61].

In contrast, a study of 3173 CML patients using a Swedish database failed to show a significant difference in 5-year relative survival in patients aged ≥80 years who received imatinib versus those who did not [62], though use of imatinib in this patient cohort was low (<20%). Another study using the SEER database to identify 8329 CML patients failed to show a significant difference in 5-year relative survival amongst patients aged ≥65 years who received imatinib versus those who did not [63], though again the authors note low imatinib use in the patient cohort. No prospective, randomized studies

have examined TKI use for elderly CML patients, and the use of second-generation TKIs in the elderly has not been well studied.

In this population it is reasonable to initiate treatment with a tyrosine kinase inhibitor but consideration can be given to using a lower dose up front or, if starting at the standard dose having a low threshold for dose reductions as long as there is evidence of some degree of molecular response.

Vascular Risk Assessment for Patients on TKI Therapy

All patients on TKI therapy should have a vascular risk assessment done including the presence of obesity, hypertension, diabetes, hyperlipidemia and smoking. A Framingham risk score should be calculated. A link is included here. All attempts should be made to mitigate risk factors, particularly if a TKI with a higher incidence of vascular events is to be utilized. This includes smoking cessation and weight loss as necessary as well as regular physical activity, achieving a calculated-LDL of < 2.0 mmol/L, a HgB A1C of , 6%, a BP of ,140/90 or 130/80 in diabetic patients and consideration of antiplatelet therapy [64,65]. This may require the involvement of the patient's family physician, an internist or a cardiologist as indicated.

Adherence

Adherence to imatinib therapy is critical in CML patients in order to achieve MMR. A prospective study examining 87 CML patients for imatinib adherence with microelectronic monitoring reported MMR (defined as 3-log reduction in BCR-ABL1 transcript levels) in 94.5% of adherent patients (adherence ≥90%) versus only 28.5% ($p<0.001$) of patients who were not adherent (adherence <90%) [19]. This has not been studied in the second generation TKI's but the concept applies.

Management of Pleural Effusion for Patients on Dasatinib

The underlying mechanism(s) of dasatinib-related pleural effusion remains unclear, and are likely multifactorial [54]. Patients over the age of 65 years are more likely to experience fluid retention events, and should be monitored closely [76]. Factors significantly related to the development of pleural effusion while on dasatinib include: a history of cardiac disease, hypertension, hypercholesterolemia, history of autoimmune disease, and history of skin rash during dasatinib or imatinib therapy [52,54]. Patients should be educated on how to recognize and report pleural effusion-related symptoms such as chest pain, dyspnea and dry cough. A small study (n=48) reported all patients experiencing dasatinib-related pleural effusion reported dyspnea, the degree of which correlated with the radiographic extent of pleural effusion [52]. Recently, it has been proposed that those patients who experience pleural effusion while on dasatinib experience superior treatment outcomes (MMR and CCyR rates) compared to those patients who do not, however, further investigations with larger sample sizes are required [77].

CML patients who exhibit symptoms of pleural effusion should undergo chest x-ray to confirm the event and to assess the severity. Generally, pleural effusions are managed with diuretics (and/or steroids), supportive measures and dose reduction, interruption, or discontinuation. In certain

circumstances, an echocardiogram may be appropriate to assess left ventricular ejection fraction (LVEF) [78,79]. Severe pleural effusion may require thoracentesis and oxygen therapy.

Once the pleural effusion has resolved it is appropriate to re-challenge with dasatinib in the absence of the previous inciting factor (s). In this setting a dose reduction may be considered. In the setting of recurrent or Grade IV effusions it may be necessary to proceed to an alternate therapeutic agent.

Management of Cytopenias in Patients on Tyrosine Kinase Inhibitors (TKIs) [78]

Upon initiation of TKI therapy one can expect a drop in peripheral blood counts upon initation of front-line therapy or when switching for resistance.

Imatinib

For patients in chronic phase imatinib should be held for an ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L. A CBC should be checked weekly and the drug reintroduced when the counts have recovered. If this happens more than once a dose reduction should be considered. In accelerated phase and blast phase, patients may have cytopenias related to disease. If cytopenia is unrelated to disease, reduce dose to 400 mg. If cytopenia persists for 2 weeks, reduce further to 300 mg. If cytopenia persists for 4 weeks, stop imatinib until ANC ≥1.0 x 10^9/L and platelet count ≥20 x 10^9/L and then resume treatment at 300 mg. Growth factors can be used in combination with imatinib for patients with resistant neutropenia [80].

Nilotinib

In chronic or accelerated phase if ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L hold nilotinib and monitor blood counts. Resume within 2 weeks at prior dose if ANC ≥1.0 x 10^9/L and platelet count >50 x 10^9/L. If blood counts remain low for >2 weeks, consider a dose reduction. Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.

Dasatinib

In chronic phase dasatinib should be held for an ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L. A CBC should be checked weekly and the drug reintroduced when the counts have recovered. If this happens more than once a dose reduction should be considered. In accelerated phase and blast phase, ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold dasatinib until ANC ≥1.0 x 10^9/L and platelet count ≥20 x 10^9/L, and resume at original starting dose. If recurrence, hold dasatinib until ANC ≥1.0 x 10^9/L and platelet count ≥20 x 10^9/L, and resume dasatinib at a reduced dose: 100 mg/day (second episode) or 80 mg/day (third episode). If cytopenia is related to CML, consider dose escalation to 180 mg/day. Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.

Bosutinib

After initiation, bosutinib should be held if ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L until ANC ≥1.0 x 10^9/L and platelet count ≥50 x 10^9/L. If recovery occurs within 2 weeks, continue bosutinib at the same dose. If blood counts remain low for greater than 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses below 300 mg/day have not been evaluated. Growth factors can be used in combination with bosutinib for patients with resistant neutropenia and thrombocytopenia.

Ponatinib

Ponatinib should be held if ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L, at which point therapy can be resumed at initial dose (usually 45mg). If ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L (i.e. second occurrence) hold ponatinib until recovery (ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L) and resume therapy at 30 mg. If third occurrence (ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L) hold ponatinib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L, and resume at 15 mg. Growth factors can be used in combination with ponatinib for patients with resistant neutropenia and thrombocytopenia.

VI. Monitoring Treatment Response

Response assessments should be categorized either as an optimal response or as treatment failure as summarized in Table 3; this excludes the category of suboptimal response in the European LeukemiaNet ELN guidelines [2,81]

The recommended definitions of optimal treatment response on TKIs for both first and second line therapy are:

First-line:

- BRC-ABL1 ≤10% (at least 1-log reduction) at 3 months
- BRC-ABL1 <1% (2-log reduction) at 6 months
- BRC-ABL1 ≤0.1% (3-log reduction) at 12 months, and thereafter

The recommended definitions of treatment failure on TKIs for both first and second line therapy are:

- *First-line:* Non-CHR and/or BCR-ABL > 10% if confirmed within 1-3 months
- BCR-ABL1 >10%
- BCR-ABL1 >1%
- Thereafter, loss of CHR, confirmed loss of CCA/Ph+ or MMR (on two consecutive tests of which BCR-ABL1 transcripts level rise by ≥1% in at least 1 test)

Table 3. Response and failure during first-line TKI therapy [81]

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR4).
A change of treatment may be considered if MMR is not reached by 36–48 months.
NA not applicable, ACA additional chromosome abnormalities in Ph+ cells, ELTS EUTOS long term survival score.
aLoss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

Studies have indicated that a more rapid and deeper molecular response is associated with a lower risk of treatment failure. An analysis of IRIS trial data found poorer event-free survival (EFS) and progression rates if BCR-ABL transcript levels were >10% at 6 months and >1% at 12 months; 7-year EFS was 95% if patients achieved MMR (*BCR-ABL* ≤ 0.1%) by 18 months [82]. In the German CML Study IV of imatinib, a cut-off value of a 1-log reduction (10%) in *BCR-ABL* transcript levels at three months was a highly significant predictor of treatment failure and disease progression [75]. A single-centre analysis reported that patients treated with first-line imatinib followed by a second-generation TKI with transcript levels >9.84% at 3 months had a significantly lower 8-year probability of OS (56.9% vs. 93.3%) compared to those with lower transcript levels; a cut-off of >9.54% at 3 months was predictive of poorer 8-year PFS (57.0 vs. 92.8%) [83].

In the DASISION trial, a reduction in *BCR-ABL* transcripts to ≤10% at three months with either front-line dasatinib or imatinib was associated with a greater likelihood of achieving CCyR by 12 months and MMR by 24 months [84]. The same ≤ 10% cut-off value at three months was predictive of achieving CCyR and MMR at two-year follow-up in the UK SPIRIT 2 study of front-line dasatinib and imatinib [85].

Peripheral blood Q-RT-PCR should be performed every 3 months. If a molecular response greater than 4.5-log reduction (MMR] is reached and stable for 2 years, the frequency of Q-RT-PCR may be decreased to every 4-6 months. Bone marrow karyotyping may be employed as an alternative to Q-RT-PCR until CCyR (<1% IS) is achieved. Bone marrow karyotyping should be considered at 1 year to confirm CCyR and to detect clonal progression or other abnormalities. Thereafter, marrow karyotyping does not need to be performed annually unless there are clonal abnormalities that need to be followed.

Monitoring should be consistently performed using the same medium (blood or bone marrow) since transcript levels can be different within these compartments, even when the sample is taken at the

same time. A variation of more than 0.5 log may be seen because of the change in compartment rather than a change in disease biology.

Mutation Testing

Mutation in the *ABL1* kinase domain (KD) is one of several mechanisms of resistance. *BCR-ABL1* mutations impair imatinib binding to the ATP site to varying degrees. Mutations are more commonly found in the context of secondary resistance but have been documented in about 30% of early CP-CML [85]. Primary resistance to imatinib is rare but is more common in advanced CML [86]. More than 90 mutations in the KD of *BCR-ABL1* have been described and associated with varying levels of drug resistance. Some mutations confer drug resistance and are associated with disease relapse. Some mutations confer clinical insensitivity to second-generation TKIs.

Mutation testing is recommended in TKI-treated patients upon failure to achieve CHR at three months, at least a 1-log reduction at six months, 2 log reduction at 12 months, or any sign of loss of response: hematologic relapse; relapse to Ph-positivity; or an increase in *BCR-ABL* transcript ratios with a 0.5 log (3.2-fold) increase in two successive samples and loss of MMR. Mutational analysis should always be performed before switching TKIs.

Mutational status and specific mutations may influence therapy after imatinib failure (see Table 4). Patients presenting with F317L/V, Q252H, or V299H mutations have a lower incidence of favourable response when treated with dasatinib, whereas patients with E255K/V, Y253H, or F359C/V respond sub-optimally to nilotinib [87]. Other, novel, mutations are regularly discovered and sensitivies should be researched if available. The presence of these specific mutations may guide the choice of a second-generation TKI in imatinib-resistant patients. Other factors, such as comorbidities, tolerability, drug availability, physician and patient preference should also be considered. Table 1 presents comorbidities predicting adverse events during treatment the various TKI's.

Table 4. *In vitro* sensitivity of various BCR-ALB1 gene products to Imatinib, Nilotinib, Dasatinib, Bosutinib, and Ponatinib. Adapted from Deininger et al. [124].

Therapy	Contraindicated mutations
Bosutinib	*T315I, V299L, G250E or F317L*
Dasatinib	*T315I/A, F3171L/V/I/C or V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I or G250E*
Ponatinib, Omacetaxine, allogeneic HCT, or clinical trial	None

VII. Treatment Resistance

Imatinib resistance

Imatinib Dose Escalation.

Two retrospective analyses have reported favourable outcomes with imatinib dose escalation in CP-CML patients with inadequate response to standard-dose imatinib therapy [25,87]. In the IRIS cohort study, at 12 months, 40% of subjects achieved their previously failed clinical milestones [25]. However, several small studies have questioned the durability of response after imatinib dose escalation in CP-CML patients with an inadequate response to conventional dosing [8,88]. Since the majority of cytogenetic response occurs within the first six months of treatment with imatinib, investigators noted that it would not be unreasonable to at consider dose escalation for inadequate initial cytogenetic response. Alternatively, the need for subsequent treatment, such as a second-generation TKI or allogeneic SCT, must be anticipated. Preliminary results from the ENESTcmr phase III trial and the ENABL study suggest that partial responders who fail to achieve a satisfactory molecular response can attain MMR after switching to a second-generation agent [89,90], although the survival advantage associated with achieving MMR has not been established. Imatinib dose escalation is therefore no longer recommended in Alberta however should be continued in patients where this has been done successfully prior to access to second generation TKI's.

Second-Generation TKIs.

In a phase II trial of nilotinib 400 mg BID in patients with imatinib resistance/intolerance, 44% achieved CCyR at 24 months; among those in CCyR, 56% went on to achieve MMR, suggesting a durable treatment response [91]. At 48 months, only 3% of patients had progressed to AP- or BC-CML. The estimated 48-month OS rate was 78% [42]. In the phase II START-C trial of dasatinib 70 mg BID in patients with imatinib resistance/intolerance, 52% achieved MCyR at 8-month follow-up, with only 2% of patients subsequently progressing after achieving MCyR [92]. At 2-year follow-up, the rates of CCyR and MMR were 53% and 47%, respectively [93].

Moreover, a study comparing dasatinib 140 mg/day with imatinib dose escalation to 800 mg/day reported significantly higher rates of CCyR (40% vs. 16%) and MMR (16% vs. 4%) with dasatinib at a median follow-up of 15 months [94]. Dasatinib was also superior with respect to the rates of treatment failure (HR 0.16) and PFS (HR 0.14). While these studies employed 70 mg BID dosing of dasatinib, a phase III open-label study found that there was comparable efficacy, less toxicity and less need for treatment interruptions with a 100 mg once-daily regimen [53].

Bosutinib has been evaluated as a second-line therapy in multiple phase I/II studies [95,96]. In one study of 288 CML patients with resistance (n=200) or intolerance (n=88) to imatinib, 85% of patients achieved/maintained complete hematologic response, 59% achieved/maintained major cytogenetic response (48% had complete response), and 35% achieved major molecular response. Of those who experienced a response,>70% were maintained for at least 2-years [95]. Toxicities were primarily gastrointestinal in nature and included diarrhea (84%), nausea (45%), and vomiting (37%), which

were primarily mild to moderate, and typically occurred early during treatment but were typically transient. Thrombocytopenia (grade 3/4) was reported in 24% of patients. The second study, involving 284 patients with resistance (n=195) or intolerance (n=89) to imatinib reported complete cytogenetic response rate, newly attained in 54% of patients after treatment with bosutinib 500 mg daily or 600 mg daily (13% of patients had dose escalation to 600mg) [96]. Overall, 59% of patients discontinued bosutinib at 5 years, commonly due to adverse events (23%) or disease progression (17%). After 60 months of follow-up 44 deaths (16% of patients) were reported (10 of which were within 30 days of last bosutinib dose).

Resistance to front-line Dasatinib or Nilotinib

In the instance where there is failure of a second-generation TKI used as front-line treatment an empiric switch to a different second generation TKI (including Bosutinib) is warranted. Mutation analysis should be sent in all cases. This can help determine which of the other second generation TKI's would work best or if ponatinib or asciminib might be indicated. HLA typing of the patient and siblings should be sent in transplant eligible patients at this point with a view to possibly proceeding to a stem cell transplant in case of failure of a second agent.

Resistance to second line therapy

In the instance where there is failure of imatinib and a second generation TKI or failure or 2 second generation TKI's HLA typing of the patient and siblings should be undertaken in transplant eligible patients. In the interim, or if the patient is not transplant eligible they should be switched to ponatinib or asciminb.

Third generation TKI – Ponatinib

Ponatinib is a TKI which has activity against native and mutated BCR-ABL, including T315I, which was under investigation by the Epic trial (phase III) which compares imatinib to ponatinib in newly diagnosed CP-CML [97]. The study was terminated after randomizing 307 patients due to the observation of arterial thrombotic events in the ponatinib development program (therefore none of the prospectively defined endpoints could be analysed). Despite termination due to adverse events, at median follow-up of 5 months, ponatinib demonstrated superior efficacy in terms of patients who achieved <10% BCR-ABL at 3 months, and the percentage of patients who achieved MMR, MR^4 and $MR^{4.5}$at any time in all Sokal risk groups (all $p<0.05$). The phase II PACE trial investigated the utility of ponatinib in native/mutated BCR-ABL including T315I in heavily pre-treated (resistance to or unacceptable side effects from dasatinib or nilotinib) CML patients or Ph-positive ALL. Among 267 chronic-phase CML patients, 56% had a major cytogenetic response, 46% had a complete cytogenetic response, and 34% had a major molecular response. Responses were observed regardless of the baseline BCR-ABL kinase domain mutation status and were maintained for at least 12 months in 91% of patients; however, 9% of patients experienced serious arterial thrombotic events, resulting in a total of 12% of patients discontinuing treatment due to adverse events [98], and

therefore ponatinib use should be restricted to specific circumstances (typically T315I) due to potential adverse events.

STAMP inhibitor - Asciminib

Asciminb has a different mechanism than other TKIs, targeting both native and mutated BCR/ABL, including T315I mutants. A phase 1 study enrolled 141 patients with CP CML who had resistance or intolerance to at least 2 prior TKIs [99]. The maximum tolerated dose of Asciminb was not reached. Dose limiting toxicities included elevations in lipase and clinical pancreatitis. 92% of patients with a hematologic relapse had a complete hematologic response; 54% without a complete cytogenetic response at baseline had a complete cytogenetic response. An MMR was achieved or maintained at 1 months in 48% of evaluable patients including 8 out of 14 with resistance or intolerance to Ponatinib. The Phase III ASCEMBL clinical trial compared Asciminb to Bosutinib in third line or more.[125] 157 patients were randomized to Asciminb 40 mg twice daily vs.76 patients to Bosutinib 500 mg once daily. With a median follow up of 14.9 months the MMR at 24 weeks was 25. 5% in the asciminib group versus 13.2% in the bosutinib group with fewer events leading to treatment discontinuation in the asciminib arm.

Patient comorbidities and treatment toxicity profile

As per in front line therapy the choice of agent should be guided by it's toxicity profile and comorbidities of the patient at hand.

Use of Interferon-α.

With the availability of second-generation TKIs, IFNα should no longer be considered a second-line therapy, but could be considered in patients who are unable to tolerate a TKI and are ineligible for SCT or entry in a clinical trial, or in women who wish to become or are pregnant. There are a number of ongoing clinical trials looking at combining interferon with TKI's but no conclusive data to this point. Treatment should be employed with the guidance of a physician with clinical experience using IFNα.

Treatment response assessment

The definition of the response (milestones) to second-line treatment should be the same as to first line treatment [81]. There are limited data to suggest that patients who fail on imatinib and one of the second-generation TKIs can respond to another second-generation TKI [97,98]. However, it is unclear if a durable response is achieved [99].

VIII Other Clinical Issues

Treatment intolerance

Many patients are intolerant of CML directed therapy. These intolerances may be due to objective findings such as cytopenias, liver dysfunction, pancreatitis or pleural effusions for example or may be symptom driven. In these instances the three second generation TKI's are available in second line with asciminib available in third line and ponatinib typically only reserved for patients with intolerance and a T315I mutation.

Dose reductions.

The DESTINY study [100] looked at 174 patients who had been on Imatinib, Dasatinib or Nilotinib for 3 years or greater with a stable MMR for at least 12 months then reduced their dose to one half the standard dose. Within the first 12 months 7% of patients had a molecular recurrence, all of whom regained MMR within 4 months of full-dose TKI resumption. Recurrence was significantly lower in those who had achieved at least a MR4 vs less. Adverse symptoms improved during the first 3 months of de-escalation though not thereafter. This approach may be considered in patients with ongoing side-effects.

Discontinuing TKIs.

Several prospective studies have suggested that patients with sustained complete molecular response (CMR; defined as molecular relapse [MR]$^{>4.5}$) may be able to stop imatinib treatment [101,102]. The Stop Imatinib (STIM) trial evaluated imatinib discontinuation in 100 patients in MR$^{5.0}$ for >2 years [101]. At a median of 30 months' follow-up, there was a molecular relapse in 61 of 100 patients; 58 relapses occurred within the first seven months. It should be noted that Q-RT-PCR testing was performed monthly for the first year when patients were most vulnerable to relapse, and every 2 months thereafter. In the FILMC trial, MMR was lost in 5 of 16 patients (31.25%) after a median time off therapy of four months [103]. Two smaller studies have reported a loss of MMR in 10-50% of patients within 6-7 months of stopping imatinib [104,105]. An Australian phase II study found that while 40-50% of patients in CMR can remain in CMR after stopping imatinib, a majority still harbor residual leukemic cells [106]. Intermittent therapy has been proposed to re-achieve previous best response in patients who relapse after stopping imatinib [107].

The TWISTER trial investigated imatinib cessation in 40 chronic-phase CML patients who had sustained undetectable minimal residual disease by conventional quantitative polymerase chain reaction who were on imatinib for at least 2 years. At 24 months, the actuarial estimate of stable treatment-free remission was 47.1%. The majority of relapses occurred within 4 months of stopping imatinib, and no relapses were reported beyond 27 months (median follow-up 42 months). All patients who relapsed remained sensitive to imatinib re-treatment [108].

A Canadian study, TRAD, enrolled 118 patients into an Imatinib discontinuation study. Subjects had to have been treated for at least 3 years with at least 2 years in an MMR4.5. Those who experienced a molecular relapse were started on Dasatinib second-line. An interim analysis showed that the 12-month relapse free survival was 57%. At the time of the report 35 out of 41 patients started on Dasatinib had achieved an MMR [109].

The EURO-SKI trial [110] enrolled 758 CML patients treated with any TKI and a deep molecular response (MR^4, BCR-ABL <0.01%) for at least one year (>4 log reduction on TKI therapy for >12 months confirmed by three consecutive PCR tests) and under TKI treatment for at least 3 years were eligible for TKI cessation. A pre-specified interim analysis with a median follow up of 27 months showed a molecular relapse free survival of 61% at 6 months and 50% at 24 months. 2 patients lost MMR despite restarting TKI therapy. In the patients treated with Imatinib longer treatment duration and longer deep molecular response durations were associated with better outcomes. TKI discontinuation was associated with an estimated €22 million in cost savings.

A substantial proportion of patients report transitory musculoskeletal pain starting within weeks after TKI discontinuation. The phenomenon was described in approximately 30% of Swedish patients and is being referred to as “TKI withdrawal syndrome” [111].

Several guidelines have now been published regarding discontinuation as seen in Table5. Major determinants of success appear to be duration of therapy and duration of deep molecular response.

Table 5. When to Stop Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia[112]

Criteria	Hughes			NCCN	ESMO
	Green	Yellow	Red		
CML past history	CP only	Resistance or KD mutation	AP/BP	CP only	CP only
Sokal	Non-high	High	NA		Non-high
Response to TKI therapy	Optimal	Warning	Failure	No resistance	Optimal
BCR-ABL1 transcript	Typical	Quantifiable atypical	Not quantifiable	Measurable	Measurable
Duration TKI	≥ 8 years	3–8 years	< 3 years	≥ 3 years	≥ 5 years
DMR	≤ MR4.5	≤ MR4.0	> MR4.0	≤ MR4.0	≤ MR4.5
Duration DMR	≥ 2 years	1–2 years	< 1 year	≥ 2 years	≤ MR4 ≥ 2 years
Retreatment				Loss MMR	
PCR sensitivity	≤ MR4.5				≤ MR4.5
Frequency of monitoring	Q1M 1st 6 months, Q2–3 months			Q1M × 6, Q6W × 6M, Q3M	Q1M × 6, Q6W × 6, Q3M

Criteria	Hughes			NCCN	ESMO
	Green	Yellow	Red		
PCR result turnaround time	≤ 4 weeks			≤ 2 weeks	

We recommend that TKI discontinuation may be considered in patients who have been on TKI therapy for at least 5 years and have achieved a QPCR of >4.5 log reduction for at least 2 consecutive years. Upon discontinuation QPCR should be monitored every month for one year. If the log reduction rises by 0.5 log for 2 consecutive months or by 1 log TKI therapy should be reinstituted. If well tolerated, the previously used TKI can be reinstituted.

Pregnancy and parenting

For men taking imatinib, dasatinib, nilotinib or bosutinib there is no increased risk of congenital abnormalities in their offspring [113,114]. In women, there is evidence of teratogenicity and TKI's are contraindicated throughout pregnancy. Ideally, TKI's should be discontinued prior to conception and failing that as soon as a pregnancy is documented. In a woman with good disease control QPCR monitoring should be escalated to once a month. In instances of loss of response or in women not in good control at the time of pregnancy interferon- α should be initiated. Leukapheresis is also safe throughout pregnancy should the situation require it [115].

Role of Allogeneic SCT.

Allogeneic SCT remains a treatment option for eligible patients since it offers the possibility of a cure (estimated 15-year survival >50% [116-118]), although this needs to be balanced with risks such as mortality, graft-versus-host disease (GvHD), life-threatening infections and risk of secondary malignancy.

Due to the success of TKIs, allogeneic SCT is now a second- or third-line option following TKI failure or intolerance. A retrospective review of patients receiving imatinib or allogeneic SCT after first-line IFNα reported EFS rates of 93% versus 59%, respectively [119]. Treatment with imatinib prior to transplant has not been shown to be detrimental to outcomes if transplant-eligible patients undergo SCT as soon as there is evidence of a loss of response or treatment failure with a TKI [120-123]. It is not clear what the timing of stem cell transplantation should be in chronic phase disease. There is no data to suggest it must be done within the first year from diagnosis. Allogeneic SCT may have a preferential role in the treatment of eligible patients with advanced-phase disease CML, those with clonal chromosome abnormalities, and patients with TKI resistance/intolerance. Therefore, in accelerated and blast phase transplantation should be considered as early as possible given the proven genetic instability of the clone.

HLA typing of the patient and available siblings should be undertaken at presentation for all patients in AP or BC. In a compliant patient HLA typing should be performed in instances of failing to meet the criteria for an optimal response as outline in Table 3 and if at any time a patient loses a previously achieved response. It should also be performed any time there is a significant intolerance to at least one TKI leading to less than optimal dosing. If there are no available HLA matched siblings, high resolution typing and a preliminary search for a matched unrelated donor should be undertaken.

Regular PCR monitoring is advised since not all patients achieve complete molecular remission post-SCT. Q-RT-PCR monitoring is advised every 3 months for the first 2 years following SCT, and every 6-12 months thereafter, unless the patient is on immunosuppressive therapy. Monitoring should continue indefinitely as late relapses can occur.

References

1. Baccarani M, Dreyling M, ESMO Guidelines Working Group. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May;21 Suppl 5:v165-7
2. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, et al. European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia: 2013. Blood 2013 122(6): 872-84
3. Arber DA, Orazi A, Hasserjian R, Borowitz MJ, Calvo KR et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022; 140(1): 1200-1228
4. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984 Apr;63(4):789-799
5. Forrest DL, Trainor S, Brinkman RR, Barnett MJ, Hogge DE, Nevill TJ, et al. Cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia are correlated with Sokal risk scores and duration of therapy but not trough imatinib plasma levels. Leuk Res 2009 Feb;33(2):271-275
6. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011 Jul 21;118(3):686-692
7. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998 Jun 3;90(11):850-858
8. Marin D, Marktel S, Bua M, Szydlo RM, Franceschino A, Nathan I, et al. Prognostic factors for patients with chronic myeloid leukaemia in chronic phase treated with imatinib mesylate after failure of interferon alfa. Leukemia 2003 Aug;17(8):1448-1453
9. Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016 30(1): 48-56
10. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, et al. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol 2016 34(24): 2851-7
11. Mensink E, van de Locht A, Schattenberg A, Linders E, Schaap N, Geurts van Kessel A, et al. Quantitation of minimal residual disease in Philadelphia chromosome positive chronic myeloid leukaemia patients using real-time quantitative RT-PCR. Br J Haematol 1998 Aug;102(3):768-774
12. Hughes T, Branford S. Molecular monitoring of BCR-ABL as a guide to clinical management in chronic myeloid leukaemia. Blood Rev 2006 Jan;20(1):29-41
13. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003 Oct 9;349(15):1423-1432.
14. Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006 Jul 1;108(1):28-37
15. Branford S, Cross NC, Hochhaus A, Radich J, Saglio G, Kaeda J, et al. Rationale for the recommendations for harmonizing current methodology for detecting BCR-ABL transcripts in patients with chronic myeloid leukaemia. Leukemia 2006 Nov;20(11):1925-1930

16. Muller MC, Erben P, Saglio G, Gottardi E, Nyvold CG, Schenk T, et al. Harmonization of BCR-ABL mRNA quantification using a uniform multifunctional control plasmid in 37 international laboratories. Leukemia 2008 Jan;22(1):96-102
17. Muller MC, Saglio G, Lin F, Pfeifer H, Press RD, Tubbs RR, et al. An international study to standardize the detection and quantitation of BCR-ABL transcripts from stabilized peripheral blood preparations by quantitative RT-PCR. Haematologica 2007 Jul;92(7):970-973
18. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachee P, Berneman Z, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood 2009 May 28;113(22):5401-5411
19. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 2010 May 10;28(14):2381-2388
20. Wu EQ, Guerin A, Yu AP, Bollu VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. Curr Med Res Opin 2010 Dec;26(12):2861-2869
21. Mederios BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing Blood Reviews 2018 32(4): 289-299
22. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003 Mar 13;348(11):994-1004
23. Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 2009 Jun;23(6):1054-1061
24. Hochhause A, Larson RA, Guilhot F, Radich JP, Branford S, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med 2017 376(10): 917-27
25. Kantarjian HM, Larson RA, Guilhot F, O'Brien SG, Mone M, Rudoltz M, et al. Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer 2009 Feb 1;115(3):551-560
26. Quintas-Cardama A, Kantarjian H, Jones D, Shan J, Borthakur G, Thomas D, et al. Delayed achievement of cytogenetic and molecular response is associated with increased risk of progression among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose imatinib therapy. Blood 2009 Jun 18;113(25):6315-6321
27. Kantarjian H, O'Brien S, Shan J, Huang X, Garcia-Manero G, Faderl S, et al. Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia: need for new response definitions? Cancer 2008 Feb 15;112(4):837-845.
28. Cortes JE, Kantarjian HM, Goldberg SL, Powell BL, Giles FJ, Wetzler M, et al. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. J Clin Oncol 2009 Oct 1;27(28):4754-4759
29. Hughes TP, Branford S, White DL, Reynolds J, Koelmeyer R, Seymour JF, et al. Impact of early dose intensity on cytogenetic and molecular responses in chronic- phase CML patients receiving 600 mg/day of imatinib as initial therapy. Blood 2008 Nov 15;112(10):3965-3973.
30. Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010 Jan 20;28(3):424-430
31. Castagnetti F, Palandri F, Amabile M, Testoni N, Luatti S, Soverini S, et al. Results of high-dose imatinib mesylate in intermediate Sokal risk chronic myeloid leukemia patients in early chronic phase: a phase 2 trial of the GIMEMA CML Working Party. Blood 2009 Apr 9;113(15):3428-3434
32. Baccarani M, Rosti G, Castagnetti F, Haznedaroglu I, Porkka K, Abruzzese E, et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet Study. Blood 2009 May 7;113(19):4497-4504
33. Gafter-Gvili A, Leader A, Gurion R, Vidal L, Ram R, Shacham-Abulafia A, et al. High-dose imatinib for newly diagnosed chronic phase chronic myeloid leukemia patients--systematic review and meta-analysis. Am J Hematol 2011 Aug;86(8):657-662
34. Breccia M, Alimena G. The current role of high-dose imatinib in chronic myeloid leukemia patients, newly diagnosed or resistant to standard dose. Expert Opin Pharmacother 2011 Sep;12(13):2075-2087

35. O'Brien S, Berman E, Moore JO, Pinilla-Ibarz J, Radich JP, Shami PJ, et al. NCCN Task Force report: tyrosine kinase inhibitor therapy selection in the management of patients with chronic myelogenous leukemia. J Natl Compr Canc Netw 2011 Feb;9 Suppl 2:S1-25
36. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. Br J Cancer 2006 Jun 19;94(12):1765-1769 PubMed ID 16721371.
37. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010 Jun 17;362(24):2251-2259
38. Saglio G, LeCoutre PD, Pasquini R, Jootar S, Nakamae H, Flinn IW. Nilotinib Versus Imatinib in Patients (pts) with Newly Diagnosed Philadelphia Chromosome-Positive (Ph+) Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENESTnd 36-Month (mo) Follow-up. Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 452. Available at: https://ash.confex.com/ash/2011/webprogram/Paper39221.html. Accessed 08/5, 2014.
39. Rosti G, Palandri F, Castagnetti F, Breccia M, Levato L, Gugliotta G, et al. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. Blood 2009 Dec 3;114(24):4933-4938
40. Cortes JE, Jones D, O'Brien S, Jabbour E, Konopleva M, Ferrajoli A, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol 2010 Jan 20;28(3):392-397
41. Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. Leukemia 2013 Jun;27(6):1310-1315
42. Le Coutre P, Rea D, Abruzzese E, Dombret H, Trawinska MM, Herndlhofer S, et al. Severe peripheral arterial disease during nilotinib therapy. J Natl Cancer Inst 2011 Sep 7;103(17):1347-1348
43. Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol 2011 Jul;86(7):533-539
44. Quintas-Cardama A, Kantarjian H, Cortes J. Nilotinib-associated vascular events. Clin Lymphoma Myeloma Leuk 2012 Oct;12(5):337-340
45. Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 2013 Jun;27(6):1316-1321
46. Tokarski JS, Newitt JA, Chang CY, Cheng JD, Wittekind M, Kiefer SE, et al. The structure of Dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants. Cancer Res 2006 Jun 1;66(11):5790-5797
47. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010 Jun 17;362(24):2260-2270
48. Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012 Feb 2;119(5):1123-1129
49. Cortes JE, Jones D, O'Brien S, Jabbour E, Ravandi F, Koller C, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol 2010 Jan 20;28(3):398-404
50. Radich JP, Kopecky KJ, Appelbaum FR, Kamel-Reid S, Stock W, Malnassy G, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood 2012 Nov 8;120(19):3898-3905
51. Hjorth-Hansen H, Stenke L, Soderlund S, Dreimane A, Ehrencrona H, et al. Dasatinib induces fast and deep responses in newly diagnosed chronic myeloid leukaemia patients in chronic phase: clinical results from a randomised phase-2 study (NordCML006). Eur J Haematol 2015 94(3): 243-250
52. Quintas-Cardama A, Kantarjian H, O'brien S, Borthakur G, Bruzzi J, Munden R, et al. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007 Sep 1;25(25):3908-3914
53. Shah NP, Kantarjian HM, Kim DW, Rea D, Dorlhiac-Llacer PE, Milone JH, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008 Jul 1;26(19):3204-3212
54. de Lavallade H, Punnialingam S, Milojkovic D, Bua M, Khorashad JS, Gabriel IH, et al. Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. Br J Haematol 2008 May;141(5):745-747
55. Sillaber C, Herrmann H, Bennett K, Rix U, Baumgartner C, Bohm A, et al. Immunosuppression and atypical infections in CML patients treated with dasatinib at 140 mg daily. Eur J Clin Invest 2009 Dec;39(12):1098-1109
56. Krauth MT, Herndlhofer S, Schmook MT, Mitterbauer-Hohendanner G, Schlogl E, Valent P. Extensive pleural and pericardial effusion in chronic myeloid leukemia during treatment with dasatinib at 100 mg or 50 mg daily. Haematologica 2011 Jan;96(1):163-166

57. Cortes JE, Kim DW, Kantarjian HM, Brummendorf TH, Dyagil I, Griskevicius L, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol 2012 Oct 1;30(28):3486-3492
58. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol 2018 36(3): 231-237
59. Brunner AM, Campigotto F, Sadrzadeh H, Drapkin BJ, Chen YB, Neuberg DS, et al. Trends in all-cause mortality among patients with chronic myeloid leukemia: a Surveillance, Epidemiology, and End Results database analysis. Cancer 2013 Jul 15;119(14):2620-2629
60. Wiggins CL, Harlan LC, Nelson HE, Stevens JL, Willman CL, Libby EN, et al. Age disparity in the dissemination of imatinib for treating chronic myeloid leukemia. Am J Med 2010 Aug;123(8):764.e1-764.e9
61. Chen Y, Wang H, Kantarjian H, Cortes J. Trends in chronic myeloid leukemia incidence and survival in the United States from 1975 to 2009. Leuk Lymphoma 2013 Jul;54(7):1411-1417
62. Bjorkholm M, Ohm L, Eloranta S, Derolf A, Hultcrantz M, Sjoberg J, et al. Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. J Clin Oncol 2011 Jun 20;29(18):2514-2520
63. Brenner H, Gondos A, Pulte D. Recent trends in long-term survival of patients with chronic myelocytic leukemia: disclosing the impact of advances in therapy on the population level. Haematologica 2008 Oct;93(10):1544-1549.
64. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001 May 24;344(21):1608-1621
65. McPherson R, Frohlich J, Fodor G, Genest J, Canadian Cardiovascular S. Canadian Cardiovascular Society position statement--recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol 2006 Sep;22(11):913-927
66. Palandri F, Castagnetti F, Alimena G, Testoni N, Breccia M, Luatti S, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. Haematologica 2009 Feb;94(2):205-212
67. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002 Mar 15;99(6):1928-1937
68. Silver RT, Cortes J, Waltzman R, Mone M, Kantarjian H. Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials. Haematologica 2009 May;94(5):743-744
69. Jiang Q, Xu LP, Liu DH, Liu KY, Chen SS, Jiang B, et al. Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase. Blood 2011 Mar 17;117(11):3032-3040
70. Palandri F, Castagnetti F, Testoni N, Luatti S, Marzocchi G, Bassi S, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. Haematologica 2008 Dec;93(12):1792-1796
71. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002 May 15;99(10):3530-3539
72. Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GJ, Rosti G, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol 2009 Jul 20;27(21):3472-3479
73. Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer 2010 Aug 15;116(16):3852-3861
74. Cortes J, Kim DW, Raffoux E, Martinelli G, Ritchie E, Roy L, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia 2008 Dec;22(12):2176-2183
75. Ottmann O, Kantarjian H, Larson R, le Coutre P, Baccarani M, Rafferty T. A Phase II Study of Nilotinib, a Novel Tyrosine Kinase Inhibitor Administered to Imatinib Resistant or Intolerant Patients with Chronic Myelogenous Leukemia (CML) in Blast Crisis (BC) or Relapsed/Refractory Ph+ Acute Lymphoblastic Leukemia (ALL). Blood (ASH Annual Meeting Abstracts) 2006;108(11):Abstract 1862. Available at: http://abstracts.hematologylibrary.org/cgi/content/short/108/11/1862. Accessed 08/5, 2014.
76. Prescribing Information: Dasatinib. http://packageinserts.bs.com/pi/pi_sprycel.pdf. 2009.
77. Eskazan AE, Eyice D, Kurt EA, Elverdi T, Yalniz FF, Salihoglu A, et al. Chronic myeloid leukemia patients who develop grade I/II pleural effusion under second-line dasatinib have better responses and outcomes than patients without pleural effusion. Leuk Res 2014 Jul;38(7):781-787

78. O'Brien S, Radich JP, Abboud CN, Akhtari M, Altman JK, Berman E, et al. Chronic myelogenous leukemia, version 1.2015. J Natl Compr Canc Netw 2014 Nov;12(11):1590-1610.
79. Hochhaus A. Management of Bcr-Abl-positive leukemias with dasatinib. Expert Rev Anticancer Ther 2007 Nov;7(11):1529-1536
80. Quintas-Cardama A, Kantarjian H, O'Brien S, Garcia-Manero G, Rios MB, Talpaz M, et al. Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia. Cancer 2004 Jun 15;100(12):2592-2597
81. Hochhaus A, Baccarani M, Schiffer SC, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020 34: 966-984
82. Hughes TP, Hochhaus A, Branford S, Muller MC, Kaeda JS, Foroni L, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010 Nov 11;116(19):3758-3765
83. Marin D, Ibrahim AR, Lucas C, Gerrard G, Wang L, Szydlo RM, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012 Jan 20;30(3):232-238 84. Hochhaus A, Saglio G, Chuah C, Pavlovsky C, Garelick M, Lambert A. Dasatinib and Imatinib-Induced Reductions in BCR-ABL Transcript Levels Below 10% At 3 Months Are Associated with Improved Responses in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Analysis of Molecular Response Kinetics in the DASISION Trial. Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 2767.
85. Marin D, Hedgley C, Clark RE, Apperley J, Foroni L, Milojkovic D. Predictive value of early molecular response in patients with chronic myeloid leukemia treated with first line dasatinib. Blood (ASH Annual Meeting Abstracts) 2011 May 29;118(21):Abstract 785.
86. Soverini S, Colarossi S, Gnani A, Rosti G, Castagnetti F, Poerio A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res 2006 Dec 15;12(24):7374-7379
87. Jabbour E, Hochhaus A, Cortes J, La Rosee P, Kantarjian HM. Choosing the best treatment strategy for chronic myeloid leukemia patients resistant to imatinib: weighing the efficacy and safety of individual drugs with BCR-ABL mutations and patient history. Leukemia 2010 Jan;24(1):6-12
88. Zonder JA, Pemberton P, Brandt H, Mohamed AN, Schiffer CA. The effect of dose increase of imatinib mesylate in patients with chronic or accelerated phase chronic myelogenous leukemia with inadequate hematologic or cytogenetic response to initial treatment. Clin Cancer Res 2003 Jun;9(6):2092-2097
89. Hughes TP, Lipton JH, Leber B, Spector N, Cervantes F, Pasquini R. Complete Molecular Response (CMR) Rate with Nilotinib in Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) without CMR After 2 Years on Imatinib: Preliminary Results From the Randomized ENESTcmr Trial of Nilotinib 400 Mg Twice Daily (BID) Vs Imatinib. Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 606.
90. Ailawadhi S, Miller CB, Jillella AP, Koshy N, Tudor B, Akard LP. Effect of Nilotinib (NIL) on Molecular Response in Chronic Myelogenous Leukemia - Chronic Phase (CML-CP) Patients (pts) with a Suboptimal Molecular Response to Imatinib (IM)–ENABL Study Update. Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 2771. Available at: https://ash.confex.com/ash/2011/webprogram/Paper44550.html. Accessed 08/5, 2014.
91. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 2011 Jan 27;117(4):1141-1145
92. Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, Druker BJ, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007 Mar 15;109(6):2303-2309 PubMed ID 17138817.
93. Mauro MJ, Baccarani M, Cervantes F, Lipton JH, Matloub Y, Sinha R. Dasatinib 2-year efficacy in patients with chronic-phase chronic myelogenous leukemia (CML-CP) with resistance or intolerance to imatinib (START-C). J Clin Oncol 2008 May 20 suppl;26:Abstract 7009
94. Kantarjian H, Pasquini R, Hamerschlak N, Rousselot P, Holowiecki J, Jootar S, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: a randomized phase 2 trial. Blood 2007 Jun 15;109(12):5143-5150
95. Gambacorti-Passerini C, Brummendorf TH, Kim DW, Turkina AG, Masszi T, Assouline S, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: Minimum 24-month follow-up. Am J Hematol 2014 Jul;89(7):732-742

96. Brummendorf T, Cortes J, Khoury H, Kantarjian H, Kim D, Schafhausen P, et al. Bosutinib As Second-Line Therapy in Patients (Pts) with Chronic Phase Chronic Myeloid Leukemia (CP CML) Resistant or Intolerant to Prior Imatinib: 60-Month Update of a Phase 1/2 Study. Blood (ASH Annual Meeting Abstracts) 2014;124(21):5544.
97. Lipton J, Chuah C, Guerci-Bresler A, et al. Epic: a phase 3 trial of ponatinib compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML). Blood (ASH Annual Meeting Abstracts) 2014;124(21):519.
98. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013 Nov 7;369(19):1783-1796 PubMed ID 24180494.
99. Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med 2019 381: 2315-2326
100. Clark RE, Polydoros F, Apperley JF, Milojkovic D, Pocock C, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. The Lancet Haematology 2017 4(7): E310-E316
101. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010 Nov;11(11):1029-1035
102. Mahon F-, Rea D, Guilhot F, Huguet F, Nicolini FE, Legros L. Discontinuation of Imatinib in Patients with Chronic Myeloid Leukemia Who Have Maintained Complete Molecular Response: Update Results of the STIM Study. Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 603.
103. Rea D, Rousselot P, Nicolini FE, Legros L, Tulliez M, Giraudier S. Discontinuation of Dasatinib or Nilotinib in Chronic Myeloid Leukemia (CML) Patients (pts) with Stable Undetectable Bcr-Abl Transcripts: Results From the French CML Group (FILMC). Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 604.
104. Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood 2007 Jan 1;109(1):58-60
105. Goh H-, Choi S-, Bang J-, Kim S-, Jang E-, Kim. D. Discontinuation of Imatinib Therapy in Chronic Myeloid Leukemia Patients with Sustained Complete Molecular Response4.5 (CMR4.5). Blood (ASH Annual Meeting Abstracts) 2011;118(21):Abstract 2763
106. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Bartley PA, et al. Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. Leukemia 2010 Oct;24(10):1719-1724
107. Goh HG, Kim YJ, Kim DW, Kim HJ, Kim SH, Jang SE, et al. Previous best responses can be re-achieved by resumption after imatinib discontinuation in patients with chronic myeloid leukemia: implication for intermittent imatinib therapy. Leuk Lymphoma 2009 Jun;50(6):944-951
108. Ross D, Branford S, Seymour J, Schwarer A, Arthur C, Yeung D, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood 2013;122(4):515-522.
109. Kim DDH, Bence-Bruckler I, Forrest DL, Savoie ML, Couban S, et al. Treatment-Free Remission Accomplished By Dasatinib (TRAD): Preliminary Results of the Pan-Canadian Tyrosine Kinase Inhibitor Discontinuation Trial. Blood (2016) 128 (22): 1922. Abstract 632
110. Saussele S, Rickter J, Guilhot J, Gruber FX, Hjorth-Hansen H, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. The Lancet Oncology 2018 19(6): 747-757
111. Richter J, Soderlund S, Lubking A, Dreimane A, Lotfi K, Markevarn B, et al. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J Clin Oncol 2014 Sep 1;32(25):2821-2823
112. Laneuville P. When to Stop Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Current Treatment Options in Oncology 2018 19, 15 https://doi.org/10.1007/s11864-018-0532-2
113. Abruzzese E, Scortechini AR, Gugliotta G, Pierri I, Musoloino C, et al. Gimema Registry of Conception/Pregnancy in Adult Patients Diagnosed with Chronic Myeloid Leukemia (CML) Treated with Tyrosine Kinase Inhibitors (TKIs). Blood 2014 124(21): 1806
114. Cortes JE, Gambacorti-Passerini C, Deininger MW, Abruzese E, DeAnnuntis L, et al. Pregnancy Outcomes in Patients Treated with Bosutinib. Blood 2018 132(Supplement 1): 1729
115. Lasica M, Willcox A, Burbury K, Ross DM, Branford S, et al. The Effect of Tyrosine Kinase Inhibitor Interruption and Interferon Use on Pregnancy Outcomes and Long-Term Disease Control in Chronic Myeloid Leukemia. Leuk Lymphoma 2019 60(7): 1796-1802

116. Robin M, Guardiola P, Devergie A, Yeshurun M, Shapiro S, Esperou H, et al. A 10-year median follow-up study after allogeneic stem cell transplantation for chronic myeloid leukemia in chronic phase from HLA-identical sibling donors. Leukemia 2005 Sep;19(9):1613-1620
117. Gratwohl A, Brand R, Apperley J, Crawley C, Ruutu T, Corradini P, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica 2006 Apr;91(4):513-521
118. Zaretsky Y, Rifkind J, Lockwood G, Tsang R, Kiss T, Hasegawa W, et al. Long-term follow-up of allogeneic bone marrow transplantation for patients with chronic phase chronic myeloid leukemia prepared with a regimen consisting of cyclophosphamide, cytarabine and single-dose total body irradiation conditioning. Bone Marrow Transplant 2007 Sep;40(5):423-430
119. Bittencourt H, Funke V, Fogliatto L, Magalhaes S, Setubal D, Paz A, et al. Imatinib mesylate versus allogeneic BMT for patients with chronic myeloid leukemia in first chronic phase. Bone Marrow Transplant 2008 Nov;42(9):597-600
120. Lee SJ, Kukreja M, Wang T, Giralt SA, Szer J, Arora M, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood 2008 Oct 15;112(8):3500-3507
121. Deininger M, Schleuning M, Greinix H, Sayer HG, Fischer T, Martinez J, et al. The effect of prior exposure to imatinib on transplant-related mortality. Haematologica 2006 Apr;91(4):452-459
122. Oehler VG, Gooley T, Snyder DS, Johnston L, Lin A, Cummings CC, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007 Feb 15;109(4):1782-1789
123. Bornhauser M, Kroger N, Schwerdtfeger R, Schafer-Eckart K, Sayer HG, Scheid C, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006 Jan;76(1):9-17
124. Deininger MW, Shaw NP, Altman JK, Berman E, Bhatia R, Bhatnagar B, et al. NCCN Clinical Practice Guidelines in Oncology 'Chronic Myeloid Leukemia. Jan. 2020, Version 3.2020
125. Rea D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021; 138(21): 2031-2041

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2012.

Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, CancerControl Alberta; AP, Accelerated phase; BC, Blast crisis; CBC, Complete blood count; CCA, Clonal chromosome abnormalities; CCyR, Complete cytogenetic response; CHR, COmplete hematologic response; CML, Chronic Myelogenous Leukemia; CP, Chronic phase; CyR, Cytogenetic response; GVHD, Graft-versus-host-disease; EFS, Event-free survival; EUTOS, European Treament and Outcome Study; FISH, Fluorescence in situ hybridization; IFN, interferon; HLA, Human leukocyte antigen; IS, International scale; ISH, In situ hybridization; KD, Kinase domain; MCyR, Major cytogenetic response; MMR, Major molecular response; MR, Molecular relapse; MRD, Minimal residual disease; N/A, Not applicable; OS, Overall survival; PAOD, Peripheral arterial occlusive disease; PCgR, Partial cytogenetic response; PFS, Progression-free survival; QRT PCR; Quantitative real-time polymerase chain reaction; RR, Risk ratio; SCT, Stem cell transplant; TKI Tyrosine kinase inhibitor; WHO, World health organization.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Derek Tilley has nothing to disclose.
Dr. Lynn Savoie reports other from Jazz, other from Amgen, other from Novartis, other from Abbvie, other from Celgene, other from Pfizer, related to the work.

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