

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 two 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. Nilotinib and Dasatinib have now been approved in Alberta along-side Imatinib as first-line agents for patients newly diagnosed with CML. Other novel agents remain under investigation. Allogeneic hematopoietic stem cell transplantation is also 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 ^{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. Appendices A, B and C summarize the most current recommendations from these agencies.

The 2015, 2017 and 2020 updates incorporated new evidence from research involving tyrosine kinase inhibitors for the treatment of CML, along with general updates.

Target Population

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

Recommendations

Staging and Prognosis:

1. The staging of CML is according to the definitions set out by the World Health Organization (WHO).
2. The Sokal index and/or Hasford score are recommended for prognostication of newly diagnosed patients with CML. The European Treatment and Outcome Study (EUTOS) score can be used for patients being treated with a TKI to predict complete cytogenetic response (CCyR) at 18 months. The more recent ETLs differentiated probabilities of dying of CML better than the Sokal, Euro and EUTOS scores.
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. The third-generation drug, ponatinib, is also available in patients for whom other TKI therapy is not appropriate, including CML that is T315I mutation positive or when there is resistance or intolerance to all other TKI therapy.

6. 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.
7. All transplant-eligible patients who fail second-line TKI therapy should be evaluated for transplantation. Transplantation should be considered in patients with evidence of clonal progression by bone marrow cytogenetics.
8. Patients presenting with accelerated phase disease should be started on a TKI with early consideration given to transplantation
9. 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.
10. Interferon- α (IFN α) 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 IFN α .
11. Asciminib is available by compassionate access when all other options have been exhausted.

Monitoring Treatment Response:

12. 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 in a compliant patient may reduce 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.

14. 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 $\leq 10\%$ (at least a 1-log reduction) and or Ph+ $\leq 35\%$ at 3 months
 - BCR-ABL1 $< 1\%$ (2-log reduction) and or Ph+ 0 at 6 months
 - BCR-ABL1 $\leq 0.1\%$ (≥ 3 -log reduction) at 12 months, and thereafter

15. The recommended definition of treatment failure on first-line TKIs in accordance with European Leukemia Net guidelines, are defined as:
 - Non-CHR and/or Ph+ $> 95\%$ at 3 months
 - BCR-ABL1 $> 10\%$ and/or Ph+ $> 35\%$ at 6 months
 - BCR-ABL1 $> 1\%$ and/or Ph+ > 0 at 12 months
 - Thereafter, loss of CHR, confirmed loss of CCA/Ph+ or MMR (on two consecutive tests of which BCR-ABL1 transcripts level rise by $\geq 1\%$ in at least 1 test)

13. Compliance to TKI prescription should be assessed at every visit, particularly in those patients with a suboptimal response

14. 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.

15. Human leukocyte antigen (HLA) typing of the patient and siblings is recommended when a patient presents in AP or BC or when there is suboptimal response, loss of a previously obtained response or significant intolerance.

16. 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.

17. Second-line optimal treatment response to TKI after failure with imatinib, in accordance with European Leukemia Net guidelines, are defined as:
 - BCR-ABL1 $\leq 10\%$ (at least 1-log reduction) and/or Ph+ $< 65\%$ at 3 months
 - BCR-ABL1 $\leq 10\%$ (at least 1-log reduction) and/or Ph+ $< 35\%$ at 6 months
 - BCR-ABL1 $< 1\%$ (2-log reduction) and/or Ph+ 0 at 12 months
 - BCR-ABL1 $\leq 0.1\%$ (3-log reduction) thereafter

18. Second-line treatment failure with a second-generation TKI, in accordance with European Leukemia Net guidelines, are defined as:
- No CHR or Ph+ >95% at 3 months
 - BCR-ABL1 >10% and/or Ph+ >65% and/or new mutations at 6 months
 - BCR-ABL1 >10% and/or Ph+ >35% and/or new mutations at 12 months
 - Thereafter, loss of CHR/CCyR/PCyR or new mutations or confirmed loss of CCA/Ph+ or MMR (in 2 consecutive tests, of which one with a BCR-ABL transcripts level $\geq 1\%$)

Special topics/other clinical issues

19. 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.
20. In patients who have achieved a stable major molecular remission dose reduction may be considered in order to improve symptom burden.
20. 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 reinstated. We suggest resuming the original TKI therapy that was used in order to achieve maximal MMR prior to attempting a treatment free remission (TFR).
21. 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. Staging

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
- **Accelerated phase (AP): (One or more of the following)**
 - *Persistent or increasing WBC ($>10 \times 10^9/L$), unresponsive to therapy*
 - *Persistent or increasing splenomegaly, unresponsive to therapy*
 - *Persistent thrombocytosis ($>1000 \times 10^9/L$), unresponsive to therapy*

- *Persistent thrombocytopenia (<100x10⁹/L) unrelated to therapy*
- *20% or more basophils in the PB*
- *10-19% blasts in the PB and/or BM*
- *Additional clonal chromosomal 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*
- **Terminal blast crisis (BC) phase:** peripheral blood 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 index and/or Hasford score should be used 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 IFN α 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 IFN α 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. Recent data have shown that the deletion on the derivative 9 is not prognostic for patients on imatinib.¹⁰ 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 MRD¹¹. 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 $\text{Log} (\text{Baseline Median Ratio}/\text{Current Ratio}) = \text{log reduction}$. 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 400mg/day

All TKIs should be used with caution in any patient with a history of cardiovascular disease, notably cardiac arrhythmias. The choice of the TKI may be guided by an individual patient's comorbidities and ability to comply with the dosing regimen. In addition, in patients with high-risk disease and a low EBMT risk score, the choice between a TKI and allogeneic SCT should be discussed. However, a trial of a first-line TKI is recommended as the early response to TKI treatment can either reinforce or weaken the indication for allogeneic SCT. Table 1 presents comorbidities predicting adverse events during treatment with a second generation TKI. 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 treatment with a second-generation TKI (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 oral TKI inhibitor imatinib mesylate remains a recommended first-line treatment for all newly-diagnosed CP-CML patients who do not initially choose related-donor allogeneic SCT. 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 IFN α 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 treatment²⁴.

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 studies⁴¹⁻⁴⁴ and a prospective study⁴⁵ 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-naïve 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 nilotinib⁴¹⁻⁴⁴.

Dasatinib.

Dasatinib is a Src/Abl TKI with activity against a range of imatinib-resistant mutations. It is about 325-fold more potent than imatinib⁴⁶. Efficacy in the first-line setting was demonstrated in the phase III DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients) trial⁴⁷. 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, respectively⁴⁸. MMR rates were significantly higher with dasatinib (64% vs. 46%), with 17% versus 8% achieving a 4.5-log reduction. At three years, MMR, MR⁴, 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 arm⁵⁰.

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 patients⁵²⁻⁵⁶. 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 imatinib⁵⁷.

In the BFORE trial⁵⁸ 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 however application has been made to Health Canada for this indication.

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-users⁶⁰. 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 not⁶¹.

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 not⁶², 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 not⁶³, 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.

Accelerated-Phase and Blast-Crisis CML

Phase II trials have investigated the efficacy of front-line imatinib 400-800 mg/day in AP-CML⁶⁶⁻⁶⁹ 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 efficacy⁶⁸. 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 years⁴². 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 affected⁷⁰. 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 months⁷¹. At 48 months, 97% had discontinued imatinib, largely due to progression or lack of efficacy⁶⁸. 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 MCyR⁷³. Supportive data were obtained in a phase II trial⁷⁴. 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 patients⁷⁵. 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

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 $\geq 90\%$) 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 multifactorial⁵⁴. Patients over the age of 65 years are more likely to experience fluid retention events, and should be monitored closely⁷⁶. 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 effusion⁵². 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 required⁷⁷.

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

Imatinib

For patients in chronic phase imatinib should be held for an ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$. 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 $\geq 1.0 \times 10^9/L$ and platelet count $\geq 20 \times 10^9/L$ 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 $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$ hold nilotinib and monitor blood counts. Resume within 2 weeks at prior dose if ANC $\geq 1.0 \times 10^9/L$ and platelet count $>50 \times 10^9/L$. 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 $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$. 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 $<0.5 \times 10^9/L$ and/or platelets $<10 \times 10^9/L$: Patients may have cytopenias related to disease. If cytopenia is unrelated to disease, hold dasatinib until ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 20 \times 10^9/L$, and resume at original starting dose. If recurrence, hold dasatinib until ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 20 \times 10^9/L$, 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 $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$ until ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$. 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 $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$ until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$, at which point therapy can be resumed at initial dose (usually 45mg). If ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$ (i.e. second occurrence) hold ponatinib until recovery (ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$) and resume therapy at 30 mg. If third occurrence (ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$) hold ponatinib until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$, 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 are:

First-line:

- BCR-ABL1 $\leq 10\%$ (at least 1-log reduction) and/or Ph+ $\leq 35\%$ at 3 months
- BCR-ABL1 $< 1\%$ (2-log reduction) and or Ph+ 0 at 6 months
- BCR-ABL1 $\leq 0.1\%$ (3-log reduction) at 12 months, and thereafter

Second-line in the case of failure of imatinib:

- BCR-ABL1 $\leq 10\%$ (at least 1-log reduction) and/or Ph+ $< 65\%$ at 3 months
- BCR-ABL1 $\leq 10\%$ (at least 1-log reduction) and/or Ph+ $< 35\%$ at 6 months
- BCR-ABL1 $< 1\%$ (2-log reduction) and/or Ph+ 0 at 12 months
- BCR-ABL1 $\leq 0.1\%$ (3-log reduction) thereafter

The recommended definitions of treatment failure on TKIs are:

First-line:

- Non-CHR and/or Ph+ $> 95\%$ at 3 months
- BCR-ABL1 $> 10\%$ and/or Ph+ $> 35\%$ at 6 months
- BCR-ABL1 $> 1\%$ and/or Ph+ > 0 at 12 months
- Thereafter, loss of CHR/CCyR or confirmed loss of mutations CCA/Ph+ or MMR (on two consecutive tests of which BCR-ABL1 transcripts level $\geq 1\%$ in at least 1 test)

Second-line in the case of failure of imatinib:

- No CHR or Ph+ $> 95\%$ at 3 months
- BCR-ABL1 $> 10\%$ and/or Ph+ $> 65\%$ and/or new mutations at 6 months
- BCR-ABL1 $> 10\%$ and/or Ph+ $> 35\%$ and/or new mutations at 12 months
- Thereafter, loss of CHR/CCyR/PCyR or new mutations or confirmed loss of CCA/Ph+ or MMR (in 2 consecutive tests, of which one with a BCR-ABL transcripts level $\geq 1\%$)

Table 3. Response and failure during first-line TKI therapy⁸¹

	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 months⁸². 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 progression⁷⁵. 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 months⁸⁴. 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 imatinib⁸⁵.

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-CML⁸⁵. Primary resistance to imatinib is rare but is more common in advanced CML⁸⁶. 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 imatinib-treated patients upon failure to achieve CHR at three months, at least a 1-log reduction at six months, CCyR 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 nilotinib⁸⁷. 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 with a second generation TKI.

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	<i>T315I, V299L, G250E or F317L</i>
Dasatinib	<i>T315I/A, F3171L/V/I/C or V299L</i>
Nilotinib	<i>T315I, Y253H, E255K/V, F359V/C/I or G250E</i>
Ponatinib, Omacetaxine, allogeneic HCT, or clinical trial	None

The half maximal inhibitor concentration (IC₅₀) shown here is universally regarded as a measure of the degree of sensitivity to a *BCR-ABL1* mutant to a given TKI and is experimentally determined by quantifying the TKI concentration required to reduce by 50% viability of a Ba/F3 mouse lymphoblastoid cell line engineered to express that mutant form of BCR-ABL1. The table lists all of the *BCR-ABL1* mutants for which the IC₅₀ values of at least 2 TKIs are available. For imatinib, dasatinib, and nilotinib, ranges of IC₅₀ values were provided when differences in IC₅₀ values reported by different studies were observed. For bosutinib and ponatinib, IC₅₀ values come from a single study. Plasma drug concentrations is also given in nM. Values of plasma drug concentration are mean ± standard deviation for imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily), and ponatinib (45 mg once daily), and median (range) for bosutinib (500 mg once daily).

N.A., not available.

*Representative of the 10 most frequent mutations.

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 response⁹¹. 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 MCyR⁹². At 2-year follow-up, the rates of CCyR and MMR were 53% and 47%, respectively⁹³.

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 months⁹⁴. 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 regimen⁵³.

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-years⁹⁵. 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).

Dasatinib or Nilotinib as front-line resistance

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 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.

Third generation TKI

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-CML⁹⁷. 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, MR⁴ 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 events⁹⁸, and therefore ponatinib use should be restricted to specific circumstances (typically T315I) due to potential adverse events.

Asciminib

Asciminib 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 TKIs⁹⁹. The maximum tolerated dose of Asciminib 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 month in 48% of evaluable patients including 8 out of 14 with resistance or intolerance to Ponatinib. Asciminib is available by special access.

Use of Interferon- α .

With the availability of second-generation TKIs, IFN α 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 IFN α .

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

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 (MR⁴, 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 Table 5. 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 Leukemia¹¹²

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
<i>BCR-ABL1</i> 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
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 reinstated. If well tolerated, the previously used TKI can be reinstated.

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 it¹¹⁵.

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 IFN α 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.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Hematology Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. 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.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2021. 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 Treatment 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.