Oncology Clinical Pathways
Chronic Myeloid Leukemia (CML)

January 2025 – V1.2025

Table of Contents

Presumptive Conditions – Chronic Myeloid Leukemia

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- All forms of leukemia, except chronic lymphocytic leukemia

Gulf War and Post 9/11 Veterans

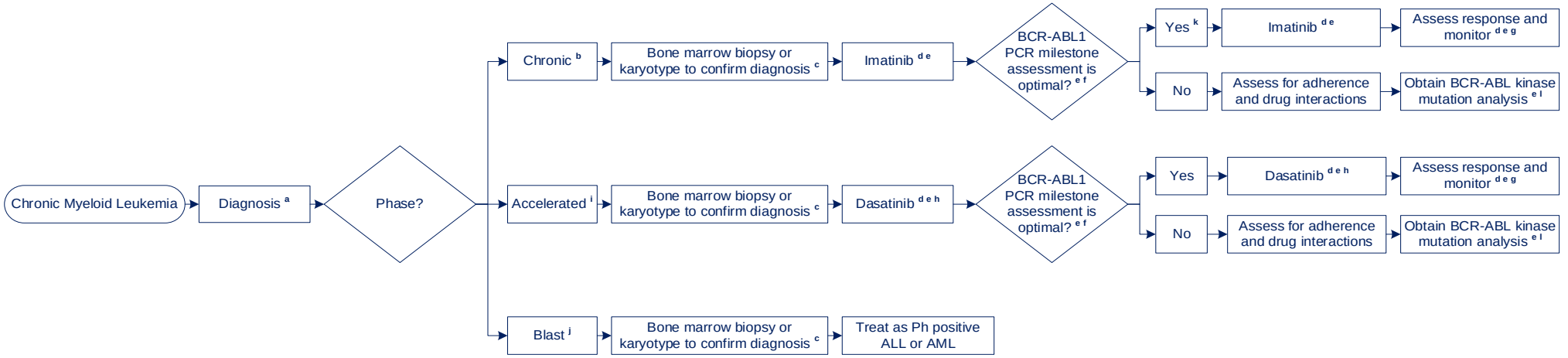
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Chronic leukemias

*The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov); VA makes several cancers presumptive for service connection Jan 08 2025; eCFR :: 38 CFR 3.320b -- Presumptive service connection for leukemias, multiple myelomas, myelodysplastic syndromes, and myelofibrosis.

Chronic Myeloid Leukemia



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Diagnosis** determined by quantitative PCR for BCR-ABL, Hepatitis B serologies, CBC metabolic panel, LDH, and uric acid; consider BCR-ABL FISH to identify alternative transcripts that may not otherwise be detected by PCR; pregnancy test for patients of child-bearing potential; pregnant patients or those wishing to become pregnant should not receive tyrosine kinase inhibitor therapy

[b] **Chronic Phase** per 2017 Who diagnostic criteria; consider starting hydroxyurea if white blood cell count is >50,000/mm^3 while awaiting diagnosis

[c] **Bone Marrow Biopsy or Karyotype** recommended in all patients to assist to differentiate chronic phase versus accelerated phase, however is not needed to initiate therapy, especially in frail patients; bone marrow biopsy is always recommended if blast phase is suspected

[d] **Assess Response and Monitor** obtain weekly CBC with differential for the first 4 to 6 weeks to monitor for cytopenias; obtain BCR-ABL1 levels via PCR every 3 months per BCR-ABL1 IS response chart; if kinase domain mutations detected, see CML Response Chart

[e] **BCR-ABL** obtain weekly CBC with diff for the first 4-6 weeks; then every 3 months to assess for cytopenia; obtain BCR-ABL levels every 3 months per chart; consider a bone marrow biopsy to assess for additional cytogenetic abnormalities

[f] **Intolerance of TKI therapy** it is appropriate to switch to another TKI if patient is not tolerating; document intolerance as an ADE in the EMR to avoid similar toxicity with a subsequent TKI

[g] **Stem Cell Transplant** Allo-HCT indications include CML patients with inadequate hematologic or cytogenetic response, resistance to TKI treatment, and intolerance of TKIs

[h] **2nd Generation TKI c**omorbidities or mutation analysis may dictate using a different 2nd generation TKI

[i] **Accelerated Phase** per ICC 2022 criteria; includes any of the following: peripheral basophils ≥20% in blood, peripheral blood or bone marrow blasts 10-19% accelerated cytogenetic abnormalities (ACA), including a second Ph chromosome, trisomy 8, isochromosome 17, trisomy 19, complex karyotype, or abnormalities of 3q26.2; consider starting hydroxyurea if white cell count is >50,000/mm^3 while awaiting diagnosis; of note fifth edition WHO no longer recognizes accelerated phase

[j] **Blast Phase** per both ICC 2022 and 5th edition WHO diagnostic criteria; peripheral blood or bone marrow blasts >20%; extramedullary myeloid sarcoma or >5% lymphoblasts; consider starting hydroxyurea if white cell count is >50,000/mm^3 while awaiting diagnosis

[k] **Discontinuation** the pros and cons of discontinuing TKI therapy must be held with all patients who are considering discontinuing therapy; see TKI Discontinuation slide

[l] **BCR-ABL1 Domain Mutation Sensitivity** BCR-ABL1 domain mutation sensitivities to TKI therapy change frequently; therefore, a comprehensive list is outside the scope of this pathway; please refer to most recent literature; the presence of T315I mutation confers resistance to all TKIs except ponatinib or asciminib; the choice of agent is guided by side effect profile and anticipated tolerance

ALL Acute Lymphoblastic Leukemia
AML Acute Myeloid Leukemia
EMR Electronic Medical Record
ICC International Consensus Classification
qPCR Real-time Polymerase Chain Reaction
TKI Tyrosine Kinase Inhibitor
WHO World Health Organization

Chronic Myeloid Leukemia – Response Chart

BCR-ABL1 (IS)	3 months	6 months	12 months
>10%	Possible TKI resistance	TKI resistant disease	TKI resistant disease
> 1% - 10%	TKI sensitive disease	TKI sensitive disease	Possible TKI resistant
> 0.1% - 1%	TKI sensitive disease	TKI sensitive disease	Provisional TKI sensitive disease
≤ .01%	TKI sensitive disease	TKI sensitive disease	TKI sensitive disease

TKI Resistant Disease
- Assess adherence and interactions with other medications
- Consider BCR-ABL1 kinase domain mutational analysis
- Consider karyotype to evaluate for additional chromosome abnormalities (ACA)s
- If no BCR-ABL1 kinase domain mutations or ACAs, then consider myeloid mutational analysis

Possible TKI Resistance
- Assess adherence and interactions with other medications
- Consider BCR-ABL1 kinase domain mutational analysis
- Consider bone marrow biopsy with karyotype analysis to assess for cytogenetic response (major cytogenetic response at 3 months or complete cytogenetic response at 12 months)
- Switch to another TKI or continue current TKI (if >50% reduction compared to baseline)
- If transplant candidate, consider referral for allogeneic transplant

Provisional TKI Sensitive Disease
- Assess adherence and interactions with other medications
- <1% is considered optimal if goal is long term survival
- If optimal, continue same TKI
- If not optimal, discuss options with patient, switching to a different TKI, referral for allogenic transplant, or a clinical trial

TKI Sensitive Disease
- Continue to monitor response every 3*6 months
- Continue to same TKI

Chronic Myeloid Leukemia – TKI Discontinuation

Discontinuing Tyrosine Kinase Inhibitor Therapy in Patients with Chronic Myeloid Leukemia

*A thorough discussion of pros and cons of discontinuing TKI therapy must be held with all patients considering discontinuing therapy

Eligibility:
- Prior evidence of quantifiable BCR-ABL1 transcript
- Continuous TKI therapy for at least 3 years
- No history of advance CML (accelerated or blast phase)
- Stable response of at least MR4 (BCR-ABL1 <0.01% IS) for at least 2 years documented on at least 4 tests performed no less than 3 months apart
- Access to qPCR testing with a sensitivity of at least MR4.5 (BCR-ABL1 <0.0032% IS) with results provided within 2 weeks
- No history of resistance to second generation TKI that required switching to a different agent

Management:
- Measurement of BCR-ABL1 by qPCR every 4 weeks for the first 6 months after discontinuing TKI therapy, then every 2 months for another 18 months
- If MR3 (BRC-ABL1 < 0.1% IS) is lost, then repeat qPCR testing 2 weeks later
    - If loss of MR3 persists, then TKI should be resumed within 2 weeks
        - Continue qPCR testing every 4 weeks until MR4 is reestablished, then every 3 months indefinitely
        - If MR4 is not reestablished, then evaluation for BCR-ABL kinase domain mutation is indicated
- If the patient remains in MR3 off TKI therapy after 2 years of qPCR testing, then monitoring should be continues at least every 6 months indefinitely given the risk of late relapse

Chronic Myeloid Leukemia – Molecular Table

Eligibility	Test Category	Test Type*	Recommended Vendors	NPOP Coverage	Specimen Type
Clinical Suspicion for Chronic Myeloid Leukemia (CML)	FISH	FISH (Bone marrow or peripheral blood) for t(9;22) BCR-ABL1	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
	Karyotyping	Bone marrow karyotype*	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
	Quantitative PCR	BCR-ABL1 quantitative PCR	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
Chronic Myeloid Leukemia (CML) in Remission	Quantitative PCR	BCR-ABL1 quantitative PCR	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
Chronic Myeloid Leukemia (CML), Relapse on TKI Therapy	Quantitative PCR	BCR-ABL1 quantitative PCR	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
	Molecular Testing	ABL1 kinase domain mutation analysis	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Blood
* Although bone marrow aspirate and biopsy are not required for diagnosis of CML, an aspirate is essential in distinguishing chronic, accelerated and blast phases and to ensure sufficient material for a complete karyotype; a bone marrow biopsy is recommended if peripheral blood findings are unusual or if a cellular aspirate cannot be obtained					