Oncology Clinical Pathways
Primary and Secondary Myelofibrosis

August 2024 – V2.2024

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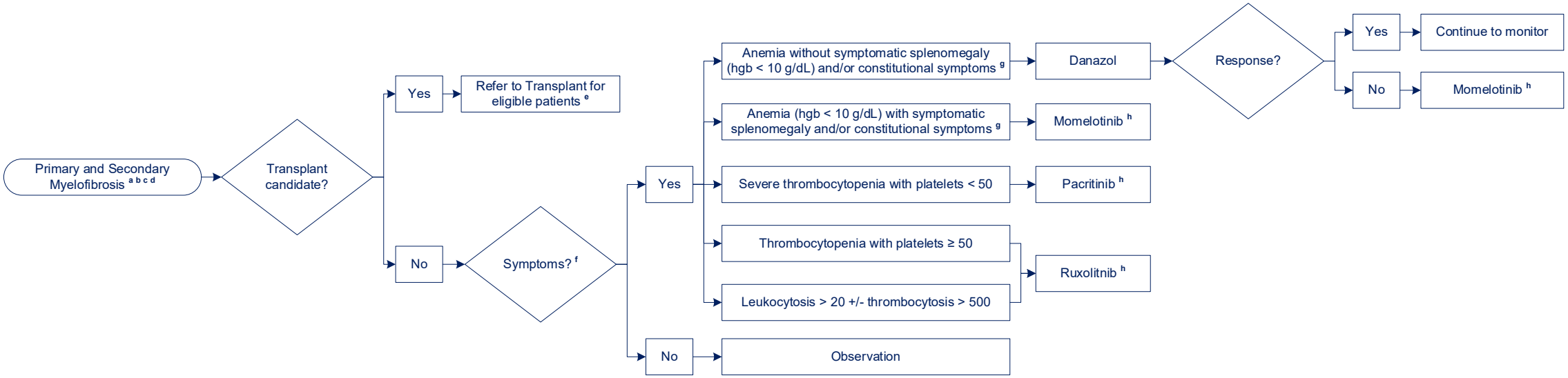
Primary and Secondary Myelofibrosis – Presumptive Conditions

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.

- Primary and Secondary Myelofibrosis are currently not presumptive conditions

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Primary and Secondary Myelofibrosis



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

[a] **Diagnosis** confirm with blood smear; evaluation with leukoerythroblastic picture and differential, including peripheral blood blasts presence of myeloid blasts in the peripheral blood is common in myelofibrosis generally not indicative of transformation to leukemia, LDH, bone marrow biopsy with reticulin stain, with aspirate smear, core and clot section with anticipation of "dry tap" or non-aspirable marrow where studies can be sent from peripheral blood; NGS testing, flow cytometry, and karyotype testing, FISH study; targeted myeloid NGS panel including ASXL1, BCOR, BCOR1, CBL, CUX1, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, KRAS, NPM1, NRAS, PHF6, RAD21, RUNX1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, ZRSR2, JAK2, CALR, MPL, SETBP1, ETNK1, PTPN11, and NF1; Optional: DDX41

[b] **Secondary Myelofibrosis** should be considered when making this diagnosis including non-malignant conditions like rheumatological disorders or other lymphoid malignancies

[c] **Spleen size** should be documented at baseline

[d] **Risk Assessment** several risk assessment tools exist including molecular features (DIPSS+, GIPSS, MIPSS70+ v2.0, MYSEC)

[e] **Transplant Eligible** initiate discussion and referral for transplant early in the course of the disease for patients age <70 years or >70 and low comorbidity index

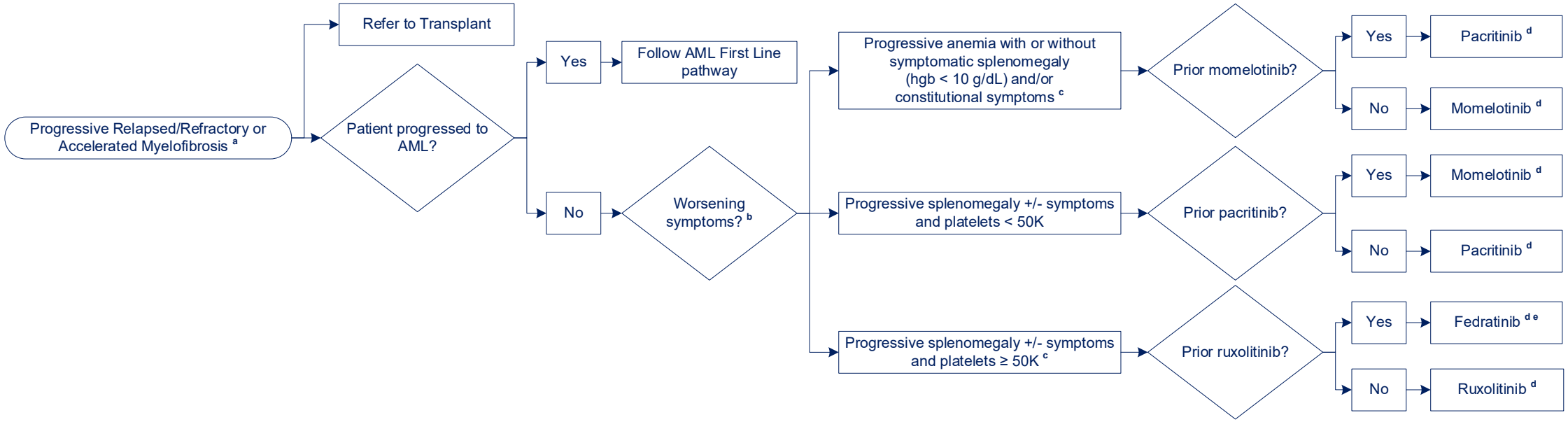
[f] **Symptoms** constitutional (fatigue, fever, night sweats, weight loss), anemia, thrombocytopenia, splenomegaly attributable myelofibrosis

[g] **Supportive Care** be mindful of iron overload in patients dependent on RBC transfusions; iron studies should be monitored and chelation therapy may be necessary; anti-platelet therapy can be continued to mitigate risk of thrombosis in the absence of moderate to severe thrombocytopenia

[h] **Responses to JAK inhibitors** can be delayed and cytopenias can worsen during initial therapy; titration of Jak 2 inhibitors to maximal tolerated dose to maximize efficacy, minimize therapy interruptions; before determining lack of efficacy, consider 3 to 6 months of uninterrupted therapy; strongly consider gradual taper when discontinuing ruxolitinib for reasons other than thrombocytopenia

JAKi Janus Kinase Inhibitors

Progressive Relapsed/Refractory or Accelerated Myelofibrosis



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

[a] **Progressive Relapsed/Refractory** signs and symptoms include rapidly enlarging spleen, worsening leukocytosis + blasts, onset of transfusion dependency, unexplained cytopenia, worsening B symptoms, clonal evolution; a bone marrow biopsy is suggested if there are concerns for progression to acute leukemia or if bone marrow biopsy results would change future management; before changing therapy, optimize dosing of current medication

[b] **Worsening Symptoms** related to underlying myelofibrosis

[c] **Supportive Care** be mindful of iron overload in patients dependent on RBC transfusions; iron studies should be monitored and chelation therapy may be necessary; anti-platelet therapy can be continued to mitigate risk of thrombosis in the absence of moderate to severe thrombocytopenia

[d] **Responses to JAK inhibitors** can be delayed, and cytopenias can worsen during initial therapy; titration of Jak 2 inhibitors to maximal tolerated dose to maximize efficacy; minimize therapy interruptions; before determining lack of efficacy, consider 3 to 6 months of uninterrupted therapy; strongly consider gradual taper when discontinuing ruxolitinib for reasons other than thrombocytopenia

[e] **Fedratinib** serious and fatal encephalopathy, including Wernicke, has occurred in patients treated with fedratinib; assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated; do not start fedratinib in patients with thiamine deficiency; replete thiamine prior to treatment initiation; if encephalopathy is suspected, immediately discontinue fedratinib and initiate parenteral thiamine; please refer to prescribing information; check thiamine level prior to initiation; serious and fatal encephalopathy, including Wernicke have occurred with fedratinib; check for and replete thiamine level prior to initiation; continue to monitor; fedratinib has a moderate to high emetogenic potential

AML Acute Myeloid Leukemia
JAKi Janus Kinase Inhibitors

Primary and Secondary Myelofibrosis – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Clinical Suspicion for Myelofibrosis	Stain	a. Reticulin stain b. Consider Trichrome stain if reticulin is moderate or marked	Local VA or locally contracted vendor	No	Bone Marrow Biopsy
	Flow Cytometry**	Flow cytometry – Leukemia/lymphoma panel	Local VA or locally contracted vendor	No	Bone Marrow Aspirate, Blood
	FISH**	FISH for t(9;22) *BCR*::*ABL1*	Local VA or locally contracted vendor	No	Bone Marrow Aspirate, Blood
	Karyotyping**	Bone marrow karyotype	Local VA or locally contracted vendor	No	Bone Marrow Aspirate, Blood
Bone Marrow Morphology Consistent with Myeloid Neoplasm with Myelofibrosis	Somatic NGS**	Targeted myeloid NGS panel including ASXL1, BCOR, BCOR1, CBL, CUX1, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, KRAS, NPM1, NRAS, PHF6, RAD21, RUNX1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, ZRSR2, JAK2, CALR, MPL, SETBP1, ETNK1, PTPN11, and NF1. Optional: DDX41.	GLA Foundation Medicine	GLA Grant*** Yes	Bone Marrow Aspirate, Blood

* Non-myeloid diseases may present with fibrosis and should be worked up as the causal disease; for example, Hairy cell leukemia, metastatic breast cancer, and classic Hodgkin lymphoma can cause marrow fibrosis but should not be worked up as a myeloid neoplasm

** Can be performed on subsequent peripheral blood sample if fresh bone marrow aspirate not available.

*** Reach out to GLA for information on use of NGS testing under a VA sponsored grant, with no cost to your local facility