

# Patterns of Ruxolitinib Therapy Failure and Its Management in Myelofibrosis: Perspectives of the Canadian Myeloproliferative Neoplasm Group

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## abstract

Ruxolitinib improves splenomegaly and other disease-related symptoms in patients with myelofibrosis, but over time, many patients lose this benefit. It is difficult to determine whether this is due to resistance or intolerance to the drug; thus, we have used the more inclusive term of ruxolitinib failure. The survival of patients with myelofibrosis after ruxolitinib failure is poor but varies significantly by the pattern of the failure, underlining the need for a clinically appropriate classification. In this review, we propose diagnostic guidance for early recognition of the pattern of ruxolitinib failure and we recommend treatment options. The most frequent patterns of ruxolitinib failure are loss or failure to obtain a significant reduction in splenomegaly or symptom response, and the development or persistence of clinically significant cytopenias. Ruxolitinib dose modification and other ancillary therapies are sometimes helpful, and splenectomy is a palliative option in selected cases. Stem-cell transplantation is the only curative option for these patterns of failure, but its restricted applicability due to toxicity highlights the importance of ongoing clinical trials in this area. Recent approval of fedratinib by the US Food and Drug Administration provides an alternative option for patients with suboptimal or loss of spleen response. The transformation of myelofibrosis to accelerated or blast phase is an infrequent form of failure with an extremely poor prognosis, whereby patients who are ineligible for transplantation have limited treatment options.

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## INTRODUCTION

Primary myelofibrosis is a rare chronic myeloproliferative neoplasm (MPN) originating from the hematopoietic stem cell. Primary myelofibrosis is characterized by cytopenias, extramedullary hematopoiesis, megakaryocytic hyperplasia, marrow fibrosis, and systemic symptoms resulting from elevated levels of inflammatory and proangiogenic cytokines. A form of myelofibrosis indistinguishable from primary myelofibrosis can occur as part of the natural history of polycythemia vera and essential thrombocythemia, referred to as post-polycythemia vera or postessential thrombocytopenia myelofibrosis. The term myelofibrosis is used in this article to include primary myelofibrosis and myelofibrosis evolved from polycythemia vera or essential thrombocytopenia.

Most patients with myelofibrosis harbor a driver mutation in the *JAK2*, *MPL*, or *CALR* genes causing dysregulation of the JAK-STAT pathway. Discovery of the *JAK2* V617F mutation paved the way for development of small-molecule inhibitors, and the first-in-class JAK inhibitor ruxolitinib was approved for use in myelofibrosis in 2011.<sup>1,2</sup> At least 10 other JAK inhibitors have entered human clinical trials

and fedratinib, pacritinib, and momelotinib have gone through phase III evaluation.<sup>3-8</sup> Development of several JAK inhibitors has been put on hold due to toxicity concerns or lack of perceived efficacy compared with ruxolitinib. In August 2019, the US Food and Drug Administration approved a second JAK inhibitor, fedratinib, for treatment of patients with myelofibrosis; however, long-term safety data on fedratinib are lacking. Ruxolitinib has the most well-characterized long-term data and safety record.

Ruxolitinib therapy improves splenomegaly- and myelofibrosis-related symptoms irrespective of JAK2 status.<sup>1,2</sup> However, its limited antitumor activity,<sup>9</sup> associated dose-limiting cytopenias, infectious complications, noncurative nature, and substantial rates of discontinuation are major concerns.<sup>10,11</sup> Weight gain can be an issue for some patients. Patients experience poor outcomes after discontinuation of ruxolitinib therapy.<sup>12-15</sup> Moreover, treatment options after ruxolitinib failure in myelofibrosis are poorly defined. A pan-Canadian collaboration, Canadian MPN Group ([www.mpncanada.com](http://www.mpncanada.com)), prepared this consensus document to provide assistance to practicing

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hematologists and oncologists on the early recognition of ruxolitinib failure and its management.

### RUXOLITINIB FAILURE: RESISTANCE OR INTOLERANCE?

There are no well-defined criteria for ruxolitinib failure. This is reflected in the varying eligibility criteria for clinical trials investigating the role of fedratinib, pacritinib, and momelotinib as second-line agents in the treatment of patients with myelofibrosis with previous exposure to ruxolitinib.<sup>6,8,16</sup> An indirect estimate of ruxolitinib failure may be inferred from treatment discontinuation rates, which vary across reported literature. Mayo Clinic investigators reported a discontinuation rate of 89% at 3 years,<sup>17</sup> compared with 50% at 3 years in the COMFORT trials,<sup>10,18</sup> which increased to 75% by 5 years.<sup>19,20</sup> These discrepancies may relate to clinical trial access allowing for a lower threshold to change treatment at suboptimal response, whereas others may continue treatment longer due to lack of effective alternatives. Also, differentiating whether failure of ruxolitinib therapy is due to resistance or intolerance is difficult (eg, cytopenias may require a reduction in dose and may indicate that a patient is intolerant to ruxolitinib). Dose reduction may result in loss of spleen and symptom response indicative of resistance. Unlike chronic myeloid leukemia, there are no molecular correlates to define JAK inhibitor therapy resistance. For these reasons, we prefer to use the broader inclusive term ruxolitinib failure rather than resistance or intolerance (Table 1). Because of overlapping features of ruxolitinib failure, pattern recognition is important for adequate treatment of these patients.

### RESPONSE ASSESSMENT TO JAK INHIBITOR THERAPY IN ROUTINE CLINICAL PRACTICE

International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria are used frequently for response assessment<sup>21,22</sup> in myelofibrosis clinical trials; however, these criteria are not used in clinical practice to assess ruxolitinib response, according to our survey of Canadian hematologists. Because complete or partial remissions are not seen with current JAK inhibitor therapy, response in routine practice is judged by the indication for therapy, such as symptomatic splenomegaly and/or myelofibrosis-associated symptoms balanced with hematologic toxicity. Volumetric assessment of spleen by magnetic resonance imaging or computed tomography scan has been the primary end point of several clinical trials but is not used in routine clinical care in Canada; splenomegaly is monitored by physical examination, and consistent spleen examination with measurement is necessary. Ultrasound is used often in patients with a difficult physical examination. Monitoring of myelofibrosis symptom response is recommended using a standardized instrument such as the MPN-10 or MPN-SAF, and evaluation of performance status.<sup>23</sup> The use of these instruments is variable outside clinical trials, and integration into routine workflow is suggested.

### PATTERNS OF RUXOLITINIB FAILURE

#### Suboptimal Spleen or Symptom Response or Loss of Response

Splenomegaly is found in 90% of patients with myelofibrosis at presentation.<sup>24</sup> In clinical trials, a significant

**TABLE 1.** Canadian MPN Group's Operational Definition of Ruxolitinib Failure

Pattern of JAK Inhibitor Therapy Failure	Definition	Expected Survival (months)	Optimization Strategy for Ruxolitinib*
Suboptimal spleen response	< 25% reduction in palpable spleen length after at least 3 months of optimally dosed JAK inhibitor therapy	14-18 <sup>13,15</sup>	Increase JAK inhibitor dose depending on Hb and platelet counts
Loss of spleen response	≥ 50% increase in spleen length from best response	14-18 <sup>13,15</sup>	Increase JAK inhibitor dose depending on Hb and platelet counts
Transfusion-dependent anemia	≥ 4 units of RBC transfusions in 8 weeks occurring ≥ 6 months from ruxolitinib treatment	8 <sup>12-15</sup>	Decrease JAK inhibitor dose
Severe thrombocytopenia	Unable to maintain unsupported platelet count > 35-50 × 10 <sup>9</sup> /L in patients receiving anticoagulation medication; and > 25 × 10 <sup>9</sup> /L in patients without anticoagulation	8 <sup>12-15</sup>	Decrease JAK inhibitor dose
Transformation to AP/BP		4-6 <sup>41-44</sup>	Continue JAK inhibitor therapy if required for splenomegaly and symptoms, dose adjustment depending on Hb and platelet counts
Second cancers		Variable	Case-by-case discussion of JAK inhibitor therapy discontinuation
Infectious complications		Variable	Consider if there would be benefit from adding prophylactic strategies to prevent recurrent infections

Abbreviations: AML, acute myeloid leukemia; AP, accelerated phase; BP, blast phase; Hb, hemoglobin; MPN, myeloproliferative neoplasms.

\*If dose-optimization strategy does not resolve the issue, consider an additional treatment strategy, per Figure 1.

spleen response was defined as a  $\geq 35\%$  reduction in spleen volume based on magnetic resonance imaging or computed tomography, which corresponds to a 50% reduction in palpable splenomegaly.<sup>25</sup> This end point was arbitrarily defined and even patients with less reduction in spleen size derive clinical benefit.<sup>26</sup> There is agreement among Canadian physicians to define ruxolitinib failure as suboptimal spleen response, with a  $< 25\%$  reduction in palpable baseline spleen length or the persistence of symptomatic splenomegaly.

In patients who once achieved a spleen response with ruxolitinib, we define a loss of response as  $> 50\%$  increase in spleen length from best-achieved response. In the setting of suboptimal response or loss of response, a careful review of dosing, compliance, and drug-drug interactions is recommended. If blood cell counts permit, the dose of ruxolitinib should be increased. Retrospective case series have shown a rechallenge with ruxolitinib after a period of interruption may result in regaining spleen response.<sup>27</sup> However, these responses are not durable in a large proportion of patients and this strategy is not recommended in routine clinical practice.

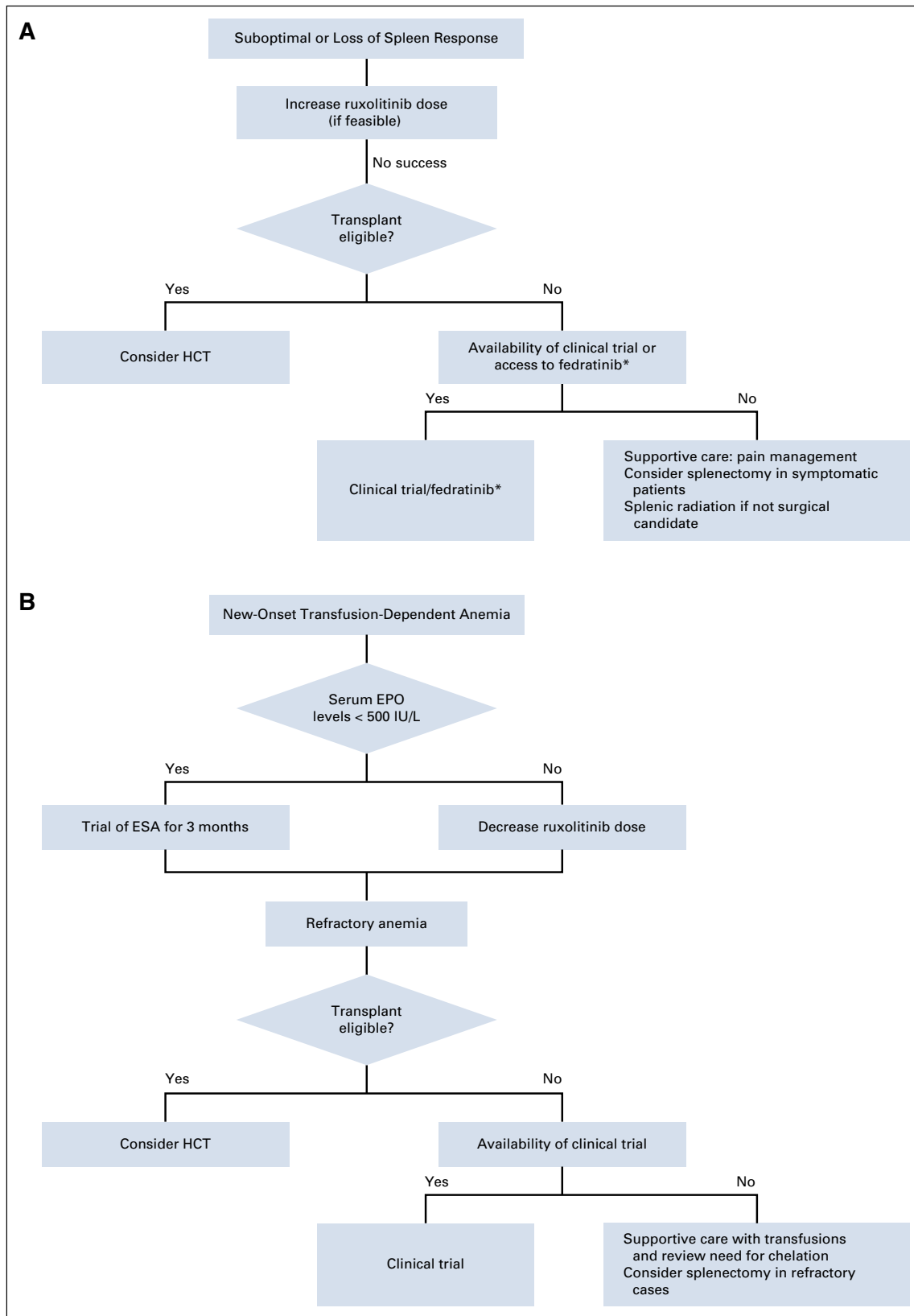
Several single and multicenter retrospective studies have indicated median survival of 14 to 18 months in patients with suboptimal or loss of spleen response to JAK inhibitor therapy.<sup>12-15</sup> Given the poor survival, consideration of hematopoietic cell transplantation (HCT) is recommended for transplantation-eligible patients (Fig 1A). We recommend that all reasonably fit patients in the transplantation age group with suitable donors should be considered for HCT. For those not eligible, enrolment into a clinical trial is strongly suggested. Clinical trial strategies include alternative JAK inhibitor therapy, combination therapy or novel agents targeting pathways other than *JAK-STAT*. Recently, the Food and Drug Administration approved a second JAK inhibitor, fedratinib, for patients with myelofibrosis. JAKARTA-2, a single-arm, phase II trial, illustrated 53% of patients who had “ruxolitinib resistance” achieved a significant spleen response ( $\geq 35\%$ ) with fedratinib.<sup>16</sup> Fedratinib is not currently available in routine clinical practice outside of the United States. Several ongoing trials (FREEDOM 1 and FREEDOM 2) are further evaluating the long-term safety and efficacy of fedratinib and will enhance our understanding of the role of fedratinib in patients with ruxolitinib failure. Other salvage therapies available in routine practice for symptomatic splenomegaly include hydroxyurea, lenalidomide, thalidomide, interferon, prednisone, and danazol.<sup>14,15</sup> However, the exact benefit of these treatment strategies is unclear.

Splenectomy is a treatment option for drug-refractory splenomegaly but carries substantial risk, with 31% and 9% morbidity and mortality rates, respectively.<sup>28</sup> The main complications are bleeding, infection, and thrombosis. Risk factors influencing survival postsplenectomy derived from 120 patients with myelofibrosis (namely, age  $> 65$  years,

transfusion requiring anemia, leukocyte count  $> 25 \times 10^9/L$ , and circulating blasts  $> 5\%$ ) were incorporated into a scoring system, which may serve as a tool for patient selection.<sup>29</sup> Splenic irradiation can be a potential alternative for patients who are considered poor candidates for splenectomy and for end-stage symptom control purposes. The effect of splenic radiation is of short duration; severe and prolonged cytopenias remain a major clinical issue.<sup>30</sup> Our approach to patients with suboptimal or loss of response to ruxolitinib therapy is summarized in Figure 1A.

### Dose-Limiting Cytopenias: Anemia

Anemia is a known on-target effect of ruxolitinib. In the COMFORT trials, anemia was observed more frequently in the ruxolitinib arms.<sup>1,2</sup> Anemia is also a major feature of progressive myelofibrosis. Given that there is no biomarker to differentiate between anemia resulting from ruxolitinib compared with anemia related to underlying myelofibrosis, clinical judgement is required. Timing of anemia and other associated symptoms helps differentiate between drug-induced versus disease-related anemia. Development of anemia in the first 12 weeks of ruxolitinib treatment is expected, and a new baseline is usually established by week 24. This anemia is self-limited and dose dependent. However, worsening anemia beyond the first 6 months of treatment may be unrelated to medication. Anemia occurring as a result of disease progression is often accompanied by an increase in myelofibrosis symptoms or splenomegaly. There was significant difference of opinion among the Canadian hematologists surveyed regarding occurrence of anemia as a marker of ruxolitinib failure. There was broader consensus that in a patient who was transfusion independent before beginning ruxolitinib treatment, transfusion-requiring anemia after 24 weeks of ruxolitinib therapy in the absence of bleeding or other causes should be considered indicative of ruxolitinib failure. Different definitions of transfusion dependence were considered, as reported in the MPN literature.<sup>21,22,31,32</sup> A study from the Princess Margaret Cancer Centre showed that transfusion-requiring anemia is associated with poor outcome irrespective of the number of transfusions,<sup>32</sup> and that patients with myelofibrosis who become transfusion dependent while receiving JAK inhibitor therapy have a median survival of 8 months.<sup>13</sup> We define transfusion dependence as at least four units of packed RBCs over 8 weeks in the absence of active bleeding or other causes. Outside the setting of clinical trials, erythropoietin-stimulating agents (ESAs), should be considered in a transfusion-dependent patient who is otherwise doing well on ruxolitinib. In the COMFORT trials, ESA use was discouraged because ESAs can activate the *JAK-STAT* pathway, potentially resulting in increased splenomegaly. A small number of patients in the COMFORT-II trial did receive both an ESA and ruxolitinib with some benefit and no compromise in ruxolitinib efficacy.<sup>33</sup> In patients who have a serum erythropoietin level  $< 500$  IU/L, a 3-month trial of



**FIG 1.** Management strategies for ruxolitinib failure. (A) Suboptimal or loss of spleen response. (B) New-onset transfusion-dependent anemia. (C) Severe thrombocytopenia. (D) Progression to accelerated phase/blast phase. (\*) Fedratinib is approved by the US Food and Drug Administration; approval is pending in other jurisdictions. AML, acute myeloid leukemia; AP, accelerated phase; BP, blast phase; EPO, erythropoietin; ESA, erythropoietin-stimulating agent; HCT, hematopoietic cell transplantation.

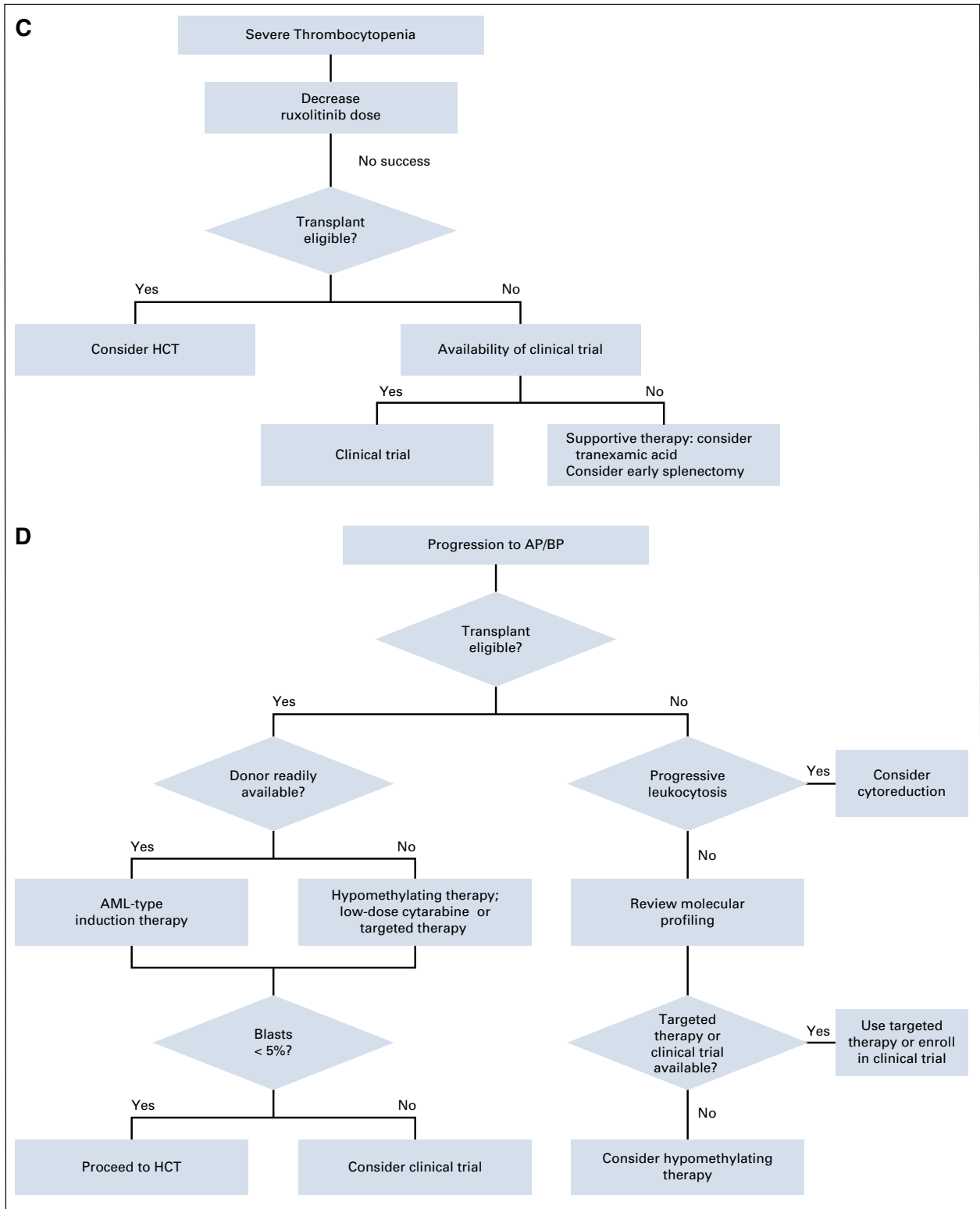


FIG 1. (Continued).

ESA is suggested. Alternatively, one can decrease the dose of ruxolitinib (Table 1; Fig 1B); however, this can result in a decrease in efficacy in symptoms and spleen response. If a minimum efficacious dose of ruxolitinib cannot be maintained, an alternative treatment strategy must be considered, including HCT or clinical trials (Fig 1B).

Other agents such as danazol,<sup>34</sup> lenalidomide<sup>35</sup> and thalidomide<sup>36</sup> have been used in combination with ruxolitinib. The studies reporting this use were limited by small sample size for any definitive conclusions to be drawn. Another JAK inhibitor, momelotinib, has shown efficacy at reducing transfusion requirements.<sup>37,38</sup> In the SIMPLIFY 2 study, researchers evaluated momelotinib compared with best available therapy in patients previously exposed to ruxolitinib.<sup>6</sup> Although the primary end point of spleen reduction was not met, 43% of patients achieved transfusion independence at week 24 compared with 21% of those receiving best available therapy. An upcoming clinical trial will further evaluate the role of momelotinib in patients with myelofibrosis who have transfusion-dependent anemia. Splenectomy may be considered as an alternative for drug-refractory anemia.<sup>29</sup>

### Dose-Limiting Cytopenias: Thrombocytopenia

Thrombocytopenia is a dose-limiting toxicity of ruxolitinib. Patients with myelofibrosis with severe thrombocytopenia are a particularly challenging subgroup. In a Spanish registry, up to 7.2% of patients with myelofibrosis had severe thrombocytopenia (platelet count  $< 50 \times 10^9/L$ ) at diagnosis.<sup>39</sup> Compared with the general myelofibrosis population, patients with severe thrombocytopenia had higher symptom burden, and higher incidence of bleeding, leukemic transformation, and death, with a median survival of 2.2 years. HCT should be considered earlier in these patients. To our knowledge, no prospective studies have been done with ruxolitinib in patients with severe thrombocytopenia (platelet count  $< 50 \times 10^9/L$ ), and clinical experience with JAK inhibitor therapy in patients with severe thrombocytopenia is limited. A lower starting dose followed by gradual upward titration is recommended for patients with platelet count  $< 100 \times 10^9/L$ .

Severe thrombocytopenia emerging while a patient is receiving a stable dose of ruxolitinib suggests disease progression and is associated with poor survival, ranging from 6 to 9 months.<sup>12,13</sup> Dose reduction or alternative therapy should be considered, though additional treatment options are limited, given platelet count restrictions in many clinical trials.

Strategies such as low-dose corticosteroids, danazol, and immunomodulators have limited efficacy data. In selected patients with drug-refractory thrombocytopenia, early consideration of splenectomy is suggested (Fig 1C).<sup>29</sup> Suggested platelet transfusion thresholds vary depending on anticoagulation needs (Table 1), and supportive care

including tranexamic acid may be required to mitigate the risk of serious bleeding.

### Transformation to Accelerated or Blast Phase

A study of 1,038 patients with myelofibrosis reported that patients with a blast percentage  $\geq 4\%$  in peripheral blood (PB) or  $\geq 5\%$  in bone marrow had poor survival similar to patients with disease in accelerated phase (AP) with blast percentage between 10% and 19%.<sup>40</sup> No consensus was reached among the Canadian MPN group for criteria defining the magnitude of change in the PB blasts warranting treatment re-evaluation. The International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria for “progressive disease” includes “bone marrow or peripheral blood blasts  $\geq 20\%$  also known as blast phase (BP), for at least 2 weeks,” but does not include AP in its definition.<sup>22</sup> Patients with myelofibrosis with PB blasts  $> 10\%$  have been excluded from prospective JAK inhibitor studies. We suggest that transformation to both AP and BP constitutes JAK inhibitor therapy failure and that these patients should be treated similarly. Median survival of patients with myelofibrosis with AP/BP is 4 to 6 months<sup>41-45</sup> and only select patients may proceed to HCT.<sup>41,43</sup> Before HCT, either intensive chemotherapy or hypomethylating agents may offer temporary disease control (Fig 1D). Intensive AML-type chemotherapy in itself has limited value unless consolidated with HCT.<sup>41,43,46</sup> We strongly recommend participation in clinical trials (Fig 1D). Given emerging therapies, a targeted myeloid gene panel analysis to identify targetable mutations should be considered.<sup>47</sup>

### Secondary Cancers

The incidence of secondary malignancies in patients treated with ruxolitinib is likely attributable to the immunosuppressive effects of ruxolitinib; the *JAK-STAT* pathway is involved in activation of many cytokines involved in anticancer surveillance. Although nonmelanoma skin cancers have been reported in patients with MPN treated with ruxolitinib,<sup>19</sup> the number of other nonhematologic, nonskin cancers is too small to determine if there is an increased risk with ruxolitinib, because of confounding factors. There is a clear increase in lymphoma in patients with MPN at baseline, which must be acknowledged in determining if ruxolitinib enhances this risk. For example, a relative increase in aggressive B-cell lymphoma of 5.8% to 9.7% of patients treated with ruxolitinib compared with 0.36% to 0.54% in control patients was reported in a study from two European centers.<sup>48</sup> By contrast, an extensive American registry study did not confirm this increase in lymphoma in patients treated with ruxolitinib compared with patients in the pre-ruxolitinib era.<sup>49</sup>

We recommend that in patients with myelofibrosis treated with ruxolitinib in whom localized basal or squamous cell carcinoma of skin develops, treatment with ruxolitinib can be continued unless multiply recurrent or aggressive. Clinically aggressive secondary cancers should be

**TABLE 2.** Useful Practice Points in Managing Ruxolitinib Failure

Serial No.	Practice Point
1	Dose optimization of ruxolitinib therapy should be attempted in patients with myelofibrosis whose disease has suboptimal response or in whom severe cytopenias develop.
2	Survival of patients with myelofibrosis after ruxolitinib therapy failure is poor and variable, depending on the cause of failure (Table 1). These patients should be clinically evaluated at an expert center if failure is suspected.
3	HCT should be considered in cases of ruxolitinib failure for transplant-eligible patients with adequate performance status. Consider earlier HCT referral in patients at high-risk for ruxolitinib failure (eg, high-risk DIPSS, RBC transfusion-dependent before ruxolitinib treatment, high-risk mutations, such as <i>ASXL1</i> and <i>EZH2</i> ).
4	Patients not eligible for transplant should be offered enrollment in clinical trials.
5	For switching patients from ruxolitinib to alternative therapy, gradual taper should be considered. Sudden discontinuation can cause withdrawal symptoms.
6	For symptomatic refractory splenomegaly, transfusion-dependent anemia, and severe thrombocytopenia, splenectomy is a useful palliative option for symptom control.

Abbreviations: HCT, hematopoietic cell transplant; DIPSS, Dynamic International Prognostic Stratification System.

discussed with medical oncologists on a case-by-case basis to determine the role for ruxolitinib discontinuation.

### Infectious Complications

The risk of opportunistic infection while receiving ruxolitinib therapy is well recognized and mediated by downregulation of *JAK1*-mediated cytokine production and impairment in dendritic cell function, resulting in impaired CD4 and CD8 T-cell function.<sup>50</sup> In a recent systematic review including five phase III randomized controlled trials (RCTs), six phase IV studies, and 28 case reports, ruxolitinib was associated with a significantly high risk of herpes zoster infection compared with the control arm in three RCTs (odds ratio, 7.39; 95% CI, 1.33 to 41.07) and in a combined analysis of extended phase III RCTs (OR, 5.20; 95% CI, 1.27 to 21.18).<sup>51</sup> In the JUMP study, the most frequent infections were herpes zoster, bronchitis, and urinary tract infections, with an incidence of 8%, 6.1%, and 6% respectively.<sup>52</sup>

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There are no guidelines on the use of anti-infection prophylactic strategies in patients with myelofibrosis requiring ruxolitinib therapy. Various Canadian MPN centers practice vaccination with Shingrix (GlaxoSmithKline, Brentford, United Kingdom) before initiating ruxolitinib therapy. We recommend treatment of active infection, followed by the appropriate prophylactic therapy for secondary prevention (eg, suppressive antiviral therapy). Before treatment, patients should receive hepatitis and HIV screening and those from endemic areas and/or with prior tuberculosis exposure or contacts be considered for tuberculosis screening. Most common infections in patients receiving ruxolitinib therapy, such as herpes or urinary tract infection, do not necessitate stopping the treatment. Serious, life-threatening infections will merit careful consideration of risks and benefits of continuing ruxolitinib therapy on a case-by-case basis.

### SWITCHING FROM RUXOLITINIB THERAPY TO ALTERNATIVE THERAPY

Discontinuation of ruxolitinib will be required in some patients needing alternative therapies such as HCT, a second-line JAK inhibitor, or participation in another clinical trial. We recommend gradual taper of ruxolitinib, given that sudden discontinuation of ruxolitinib can cause withdrawal symptoms. For transplantation patients, we recommend a slow taper over 5 days and that the last dose of ruxolitinib be taken 1 day before conditioning therapy.<sup>53,54</sup> For other patients, we recommend decreasing the dose by 5 mg twice daily per week with close monitoring of withdrawal or return of myelofibrosis-related symptoms. A short course of steroids can be helpful until a definitive alternative treatment is started.

In conclusion, the outcome of patients in whom ruxolitinib treatment fails is heterogenous and depends on the cause of failure. It is important to recognize the pattern of ruxolitinib failure, because treatment will depend predominantly on the cause. Patients with high-risk Dynamic International Prognostic Scoring System scores, transfusion requiring anemia before beginning ruxolitinib therapy, and those with high-risk mutations such as *ASXL1* and *EZH2* are at higher risk of ruxolitinib failure<sup>55,56</sup> and HCT should be considered earlier (Table 2). Several alternative therapeutic strategies are being actively investigated and participation in clinical trials is strongly recommended to make further progress in this area.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Patterns of Ruxolitinib Therapy Failure and Its Management in Myelofibrosis: Perspectives of the Canadian Myeloproliferative Neoplasm Group**

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