Myelofibrosis: Why transplant timing dictates survival, not just symptoms

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Myelofibrosis, a chronic myeloproliferative neoplasm, presents a complex management challenge. The disease course is highly variable, ranging from indolent to aggressive, with a significant risk of progression to acute myeloid leukemia. For many patients, allogeneic stem cell transplant (allo-SCT) remains the only potentially curative option, but the decision of when to refer for transplant is fraught with considerations.
The central dilemma lies in balancing the potential for long-term survival benefit against the substantial risks associated with the procedure itself. This requires a precise understanding of prognostic indicators and a willingness to act before advanced disease complicates the transplant process.

KEY TAKEAWAYS

- The Pivot: Risk stratification tools now guide earlier transplant referral for higher-risk myelofibrosis patients.
- The Data: Transplant-related mortality decreases when patients are referred before significant disease-related complications arise.
- The Action: Clinicians should integrate dynamic risk assessment into routine myelofibrosis management to identify transplant candidates proactively.

Myelofibrosis is characterised by progressive bone marrow fibrosis, extramedullary hematopoiesis, splenomegaly, and debilitating constitutional symptoms. The disease arises from clonal hematopoietic stem cells and can lead to cytopenias, infections, and ultimately bone marrow failure. While supportive care and JAK inhibitors can alleviate symptoms and improve quality of life, they do not alter the natural history of the disease in a curative sense. Allogeneic stem cell transplant, however, offers the potential for long-term remission or even cure by replacing the diseased hematopoietic system with healthy donor cells.
The decision to pursue allo-SCT is not taken lightly. It involves a rigorous assessment of patient fitness, donor availability, and disease risk. Historically, transplant was often reserved for patients with advanced disease, but this approach frequently led to worse outcomes due to the patient's deteriorating condition. The field has since shifted towards earlier intervention for those at higher risk, recognising that a healthier patient tolerates the rigours of transplant better.

Risk Stratification and the Transplant Window

Identifying the right candidates for allo-SCT hinges on accurate risk stratification. Several prognostic scoring systems exist, such as the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), and DIPSS-Plus. These systems integrate clinical features like age, hemoglobin levels, leukocyte count, blast percentage, and constitutional symptoms to predict overall survival and risk of leukemic transformation. Patients

classified as intermediate-2 or high-risk by these scores typically have a median survival measured in years, not decades, making them prime candidates for transplant consideration.

But risk scores are not static. The disease evolves, and a patient's risk profile can change over time. This dynamic nature necessitates ongoing re-evaluation. A patient initially deemed low-risk might progress to a higher-risk category due to new cytopenias, increasing blast count, or worsening constitutional symptoms. This progression often signals the opening of the optimal transplant window. Referring too early might expose a patient to unnecessary transplant risks if their disease is indolent, but waiting too long can mean the patient is too frail to undergo the procedure successfully.

The Impact of Disease Burden on Outcomes

The timing of transplant referral directly correlates with transplant-related mortality (TRM) and overall survival. Patients undergoing allo-SCT when their disease burden is lower, or before significant complications arise, generally experience better outcomes. For example, severe cytopenias, active infections, or significant organ dysfunction due to extramedullary hematopoiesis can substantially increase the risks of conditioning regimens, engraftment failure, and post-transplant complications. The management of neutropenia, for instance, becomes far more challenging in a patient already compromised by advanced myelofibrosis.

Patients with a higher blast percentage at the time of transplant also face a greater risk of relapse. While pre-transplant cytoreductive therapy can reduce blast counts, it does not always mitigate the underlying aggressive biology. The presence of adverse cytogenetics or specific molecular mutations, such as ASXL1, SRSF2, or EZH2, further complicates the picture, often indicating a more aggressive disease course and a greater need for timely intervention. These genetic markers can refine prognostic scores and help identify patients who will benefit most from early transplant referral.

Navigating Donor Selection and Conditioning Regimens

Once a patient is identified as a transplant candidate, the search for a suitable donor begins. This can involve a matched sibling donor, an unrelated donor, or a haploidentical donor. The availability of a donor, particularly a fully matched one, can influence the feasibility and timing of transplant. For patients with myelofibrosis, the choice of conditioning regimen is also critical. Myeloablative conditioning (MAC) regimens are generally associated with higher TRM but also a lower risk of relapse. Reduced-intensity conditioning (RIC) regimens offer a lower TRM but may carry a higher risk of relapse, particularly in patients with more aggressive disease. The decision between MAC and RIC is individualised, balancing the patient's age, comorbidities, and disease status. This is a complex decision, and clinicians often consult comprehensive resources like the Oxford Handbook of Clinical Haematology for guidance on these intricate protocols.

The role of JAK inhibitors, such as ruxolitinib, in the pre-transplant setting is also a point of discussion. These agents can reduce splenomegaly and constitutional symptoms, potentially improving a patient's fitness for transplant. But their impact on post-transplant outcomes is still being elucidated. Some data suggest that controlling disease burden pre-transplant with JAK inhibitors might improve engraftment and reduce post-transplant complications, but this is not a universal finding. The optimal duration and timing of JAK inhibitor use relative to transplant remain areas of ongoing investigation, as does the efficacy of JAK inhibitor combinations.

Where the Evidence Falls Short

Despite advances in risk stratification and transplant techniques, significant gaps remain. The optimal timing for transplant in patients with intermediate-1 risk myelofibrosis is less clear. These patients have a more heterogeneous

prognosis, and the benefits of early transplant may not always outweigh the risks. There is also a lack of robust, prospective data comparing different pre-transplant strategies, particularly regarding the use of JAK inhibitors. Most recommendations are based on retrospective analyses or expert consensus, which, while valuable, do not provide the same level of evidence as randomised controlled trials.

The long-term impact of transplant on quality of life, beyond survival, also requires more attention. While survival is paramount, the burden of chronic graft-versus-host disease (GVHD) and other late complications can be substantial. Understanding these long-term effects is essential for shared decision-making with patients, as it directly impacts their well-being. The field needs better tools to predict which patients will develop severe GVHD and how to mitigate it effectively. This is particularly relevant given the increasing use of haploidentical transplants, which, while expanding donor access, can carry different GVHD profiles.

The decision to pursue allogeneic stem cell transplant in myelofibrosis is not a simple one; it is a calculated risk, and timing is everything. Sarah Gellar, Clinical Trials EditorThe patient's age and comorbidities are also major determinants of transplant eligibility and outcome. While older age was once an absolute contraindication, advances in RIC regimens have made transplant feasible for some older patients. But careful patient selection remains paramount. A fit 70-year-old with few comorbidities might be a better transplant candidate than a frail 50-year-old with multiple organ dysfunctions. The assessment of fitness must be comprehensive, extending beyond chronological age to include performance status, organ function, and psychological resilience. This holistic view is essential for ensuring that the potential benefits of transplant outweigh the significant risks.

The role of minimal residual disease (MRD) monitoring post-transplant is another evolving area. Detecting residual disease early could allow for pre-emptive interventions to prevent full relapse. But standardised methods for MRD assessment in myelofibrosis are still under development. The heterogeneity of molecular mutations in myelofibrosis makes a single, universal MRD marker challenging to identify. Future research will need to focus on developing sensitive and specific MRD assays that can guide post-transplant management and identify patients who might benefit from additional therapies. This is a complex area, and the management of myelofibrosis with cytopenia highlights the need for precise monitoring.

The goal is to identify patients who will benefit most from allo-SCT and refer them at the optimal time, before their disease progresses to a point where transplant becomes too risky or ineffective. This requires a collaborative approach between haematologists, transplant physicians, and supportive care teams. The unanswered question remains how to precisely identify the individual patient's optimal transplant window, moving beyond population-level risk scores to truly personalised decision-making.

> **CLINICAL IMPLICATIONS**
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> The imperative for earlier referral in higher-risk myelofibrosis is clear. Waiting until a patient is symptomatic or has advanced disease significantly compromises transplant success, turning a potentially curative intervention into a desperate measure. Clinicians must integrate dynamic risk assessment tools into their routine practice, not just at diagnosis, but throughout the disease course.
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> The challenge lies in overcoming the inertia of observation, particularly when patients are initially stable. But the evidence suggests that a proactive approach, identifying the optimal transplant window before severe

> complications emerge, yields better outcomes. This requires open and honest conversations with patients about the risks and benefits of transplant, even when they feel relatively well.
> The field needs better predictive markers to refine this timing further, moving beyond broad risk categories to truly individualised decision-making. Until then, a vigilant approach to risk stratification and a willingness to refer for transplant consultation at the first sign of disease progression remain paramount. The goal is not just to offer a transplant, but to offer a successful one.

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