Refining risk stratification to improve prognosis in juvenile myelomonocytic leukemia

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Juvenile myelomonocytic leukemia (JMML) is a rare and aggressive myeloproliferative malignancy of early childhood. Whilst a small subset of patients may experience spontaneous remission without extensive therapy, for the majority of patients with JMML, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option.[1] Although improved over time, the prognosis of patients with JMML remains poor, with 50% of patients surviving after HSCT.[1] It is known that approximately 90% of patients with JMML will harbor mutations in one of 5 genes involved in the RAS pathway: *NF1*, *NRAS*, *KRAS*, *PTPN11* and *CBL*.[2,3] Additional genes associated with JMML in a small percentage of cases include *ASXL1*, *SETBP1* and *JAK3* mutations.[2,4] Our understanding of the genomic landscape of JMML has improved over time, and we now know that the number of RAS-pathway mutations,[3,4] RAS double pathway mutations,[3,4] and high methylation status[2] are all associated with a poor prognosis.

In this issue of *Haematologica*, Meyran *et al.*[5] retrospectively report the outcomes of 119 children diagnosed with JMML who had genetic characterization and underwent HSCT over a 20-year period. Overall, outcomes in their cohort had improved in comparison with historical data, with 5-year overall survival (OS) of 73.6% (95% CI: 65.7-82.4), 5-year event-free survival (EFS) 66.4% (95% CI: 58.2-75.8), treatment-related mortality (TRM) 9% (95% CI: 4.6-15.3), and 5-year cumulative incidence of relapse 24.6% (95% CI: 17.1-32.8). Meyran *et al.*[5] go on to report on a predictive model of clinical and genetic factors to prognosticate outcomes post HSCT. Four adverse prognostic factors were identified. These included: age at diagnosis ≥2 years, time from diagnosis to HSCT ≥6 months, monocyte count at diagnosis >7.2x10^9/L, and the presence of ≥1 additional genetic alterations (Figure 1). The more of these factors present, the lower the 5-year OS, with patients with 3 or more of these factors having an OS of 34.2%, and those with none of these factors having a 5-year OS of 100%. Interestingly, previously reported prognostic factors[2] including platelet count, elevated fetal hemoglobin for age, elevated bone marrow blast percentage, and abnormal karyotype were not found to significantly influence outcome. Consideration of additional genetic factors now known to affect prognosis, such as DNA hypermethylation,[3] were not evaluated as part of this model, and will need to be considered as more about this rare disease is known.

The model provided by Meyran *et al.*[5] begs a question: if we can, indeed, identify a cohort of patients who are at heightened risk of poor outcomes post HSCT, then how would we intervene? Furthermore, in those patients with no or minimal risk factors, can we avoid HSCT altogether? The potential interventions for high-risk patients include pre-HSCT treatment, optimising approaches to HSCT, and adding post-HSCT therapy. There have been a wide variety of approaches to pre-HSCT treatment of JMML, including observation, low-dose chemotherapy, and acute myeloid leukemia (AML)-like style chemotherapy, but so far none of the standard chemotherapy regimens used have been shown to have a significant impact on post-HSCT outcomes.[2,6] Meyran *et al.*[5] did not find that EFS or relapse incidence was significantly affected by the chemotherapy regimen given prior to HSCT, recognizing that new therapies such as azacitadine, a DNA hypomethylating agent, could not be compared within this cohort due to its infrequent use. The role of azacitidine in pre-HSCT therapy for JMML was explored in the JMML-001 trial,[7] which evaluated monotherapy with azacitidine prior to HSCT in 18 patients with newly diagnosed JMML. After 3 cycles, 61% of patients exhibited a partial response, and 14 achieved complete remission (CR) after HSCT during a 2-year follow-up. Trametinib, a MEK 1/2 inhibitor, was evaluated in the Children's Oncology Group (COG) ADVL1521 trial in 9 patients with relapsed/refractory JMML[8] and 4 had an objective response, with a favorable side-effect profile.

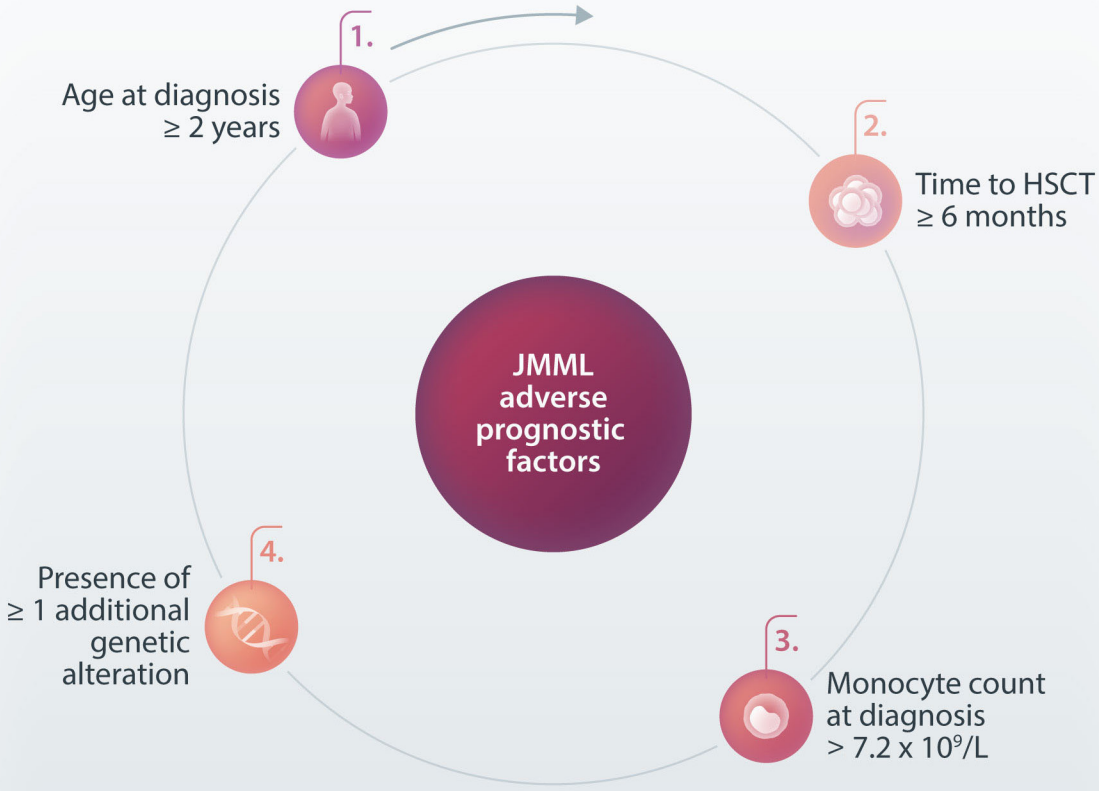

Figure 1. Adverse prognostic factors in juvenile myelomonocytic leukemia.

A phase I/II trial (*clinicaltrials.gov identifier: 05849662*) is currently underway and will assess the combination of trametinib with azacitidine in low-risk patients (those with one somatic alteration and low DNA methylation) without HSCT and in combination with fludarabine/cytarabine in high-risk patients (more than one somatic alteration or intermediate/high DNA methylation) as pre-HSCT therapy.[9] Optimising HSCT approaches has also been explored, most recently in relation to the type of conditioning used. The data suggest that the intensity of conditioning matters in JMML, with attempts at reducing the intensity of conditioning with busulfan and fludarabine (Bu/Flu) resulting in higher rates of relapse when compared with the combination of busulfan, cyclophosphamide and melphalan (Bu/Cy/Mel).[10] Similar findings were seen in the study of Meyran *et al.*,[5] with Bu/Flu/Mel and Bu/Cy/Mel having similar EFS and OS, but any other form of conditioning being associated with a reduction in EFS. Lastly, whether there is a role for targeted and novel therapies as post-HSCT treatment in those identified to be at high risk for relapse is a question still to be answered.

The article by Meyran *et al.*[5] sheds further light on the factors which can influence the risk of relapse in patients with JMML. It encourages clinicians to incorporate contemporary risk stratification models, including comprehensive molecular characterization and methylation status, in their practice. However, it also raises further questions. Their prognostic model may help us identify those at risk of relapse post HSCT and those who may not require HSCT, but what can we then do with this information? For those with none of these prognostic factors, then perhaps an active 'watch and wait' approach can be adopted. In those at high risk, and where clinically indicated, we could ensure patients undergo HSCT early, ideally within six months. As we gain more understanding of the molecular landscape of JMML, further exploration of the role of novel agents, such as hypomethylating agents, MEK inhibitors, JAK inhibitors and tyrosine kinase inhibitors, will need to be evaluated as potential options to target high-risk populations or reduce treatment intensity in those at low risk of relapse.

Disclosures

No conflicts of interest to disclose.

Contributions

JLN and CJF wrote the manuscript.

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