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Refining risk stratification to improve prognosis in juvenile myelomonocytic leukemia

In response to: A predictive classifier of poor prognosis in transplanted patients with juvenile myelomonocytic leukemia: a study on behalf of the SFGM-TC.

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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 five 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, 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 were improved from 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 a predictive model of clinical and genetic factors to prognosticate outcomes post-HSCT. Four adverse prognostic factors were identified and 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 (see Figure 1). The more of these factors present, the lower the 5-year OS, with patients with three 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 HbF 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 is learnt about this rare disease.

Meyran et al’s\(^5\) model begs the question, if we can identify a cohort of patients who are at heightened risk of poor outcomes post HSCT, then what can we do in this group of patients to intervene? Furthermore, in those 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 AML-style chemotherapy, but to date no standard chemotherapy regimens used have been shown to have a significant impact on post-HSCT outcomes.\textsuperscript{2, 6} Meyran et al.\textsuperscript{5} did not find that EFS or relapse incidence was significantly affected by the chemotherapy regimen given prior to HSCT, recognising that new therapies such as azacitadine, a DNA hypomethylating agent, were not able to be compared within this cohort due to infrequent use. The role of azacitadine in pre-HSCT therapy for JMML was explored in the JMML-001 trial,\textsuperscript{7} which evaluated monotherapy with azacitadine prior to HSCT in 18 patients with newly diagnosed JMML. After three 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 COG trial ADVL1521 in nine patients with relapsed/refractory JMML\textsuperscript{8} and four had an objective response, with a favourable side effect profile. A current phase I/II trial (NCT05849662) is being conducted assessing the combination of trametinib with azacitadine 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.\textsuperscript{9} Optimising HSCT approaches has also been explored, most recently in relation to the type of conditioning used. The data suggests that the intensity of conditioning matters in JMML, with attempts at reducing 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).\textsuperscript{10} Similar findings were seen in Meyran et al.’s study\textsuperscript{5}, with Bu/Flu/Mel and Bu/Cy/Mel having similar EFS and OS, but any other forms of conditioning were associated with a reduction in EFS. Lastly, whether there is a role of targeted and novel therapies as post-HSCT treatment in those identified at high risk for relapse is a question still to be answered.

The article by Meyran et al.\textsuperscript{5} sheds further light on understanding the factors which can influence the risk of relapse in patients with JMML and encourages clinicians to incorporate contemporary risk stratification models including comprehensive molecular characterization and methylation status in their practice. However, it also raises more 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 adapted. In those at high risk, and where clinically indicated, we could ensure HSCT occurs early, ideally within six months. As we gain more understanding of the molecular landscape of JMML, further exploration of the role of novel agents e.g., 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.
References

Figure 1. Adverse prognostic factors in JMML.
JMMML adverse prognostic factors

1. Age at diagnosis $\geq 2$ years
2. Time to HSCT $\geq 6$ months
3. Monocyte count at diagnosis $\geq 7.2 \times 10^9/L$
4. Presence of $\geq 1$ additional genetic alteration