A double punch for plasma cell leukemia

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The recent approval of multiple novel therapies for multiple myeloma makes it easy to forget that primary plasma cell leukemia (pPCL) remains a heavily understudied cancer with limited evidence-based treatment options. Its rare occurrence and the clinical urgency to start therapy, among other factors, have been substantive barriers to randomized trials for pPCL patients.

In this data-deprived context, the work by Lawless, Iacobelli and colleagues published in this issue of *Haematologica* offers highly welcome retrospective evidence from the European Group for Blood and Marrow Transplantation registry, which has been providing invaluable insights into rare blood cancers such as pPCL, long before 'real-world data' came into the focus of a wider audience.[1] This analysis of 751 pPCL patients treated with single (autologous [auto] or allogeneic [allo]) or tandem transplants (auto-auto or auto-allo) between 1998 and 2014 (the 'pre-maintenance therapy era') focused particularly on the impact of tandem over single transplants, but also compared the tandem approaches, which had not been studied at this detail in pPCL before.

Adjusting for baseline characteristics, patients treated with auto-allo showed the greatest improvement in progression-free survival over those treated with single auto, while patients who underwent auto-auto showed a nominal, but non-significant improvement over those who underwent single auto. Interestingly, modeling suggested that patients in complete response after induction had longer progression-free survival with auto-auto than with auto-allo and that both of these transplantation strategies performed during complete response produced longer progression-free survival than that after single auto or auto-allo in patients not having achieved complete response post-induction. Although overall survival was nominally improved by tandem approaches, the difference over that with single auto did not reach statistical significance. While the clinically non-acceptable high and early non-relapse mortality of single allo was markedly lower with auto-allo, the long-term overall survival of patients treated with the two strategies was similar, as were acute and chronic graft-*versus*-host disease (GvHD) rates.

Intensive therapy including transplant remains standard care for younger pPCL patients in many healthcare systems - induction and maintenance therapy often being laterally adopted from myeloma practice. In this context, results from the current study are highly informative. The longer progression-free survival and, in particular, the reduced non-relapse mortality for auto-allo recipients are encouraging, and are likely to still hold up with contemporary induction therapies. Nevertheless, the majority of pPCL patients in this study still relapsed within 2-3 years after auto-allo, highlighting the general need for post-transplant maintenance strategies. Two potentially interlinked questions emerge in the context of maintenance: (i) would the advantage for auto-allo persist with maintenance? (ii) would maintenance be feasible in the context of acute and chronic GvHD after auto-allo?

While it is impossible to answer the former question without further data, there is some myeloma-derived evidence regarding the latter. For lenalidomide, the only approved maintenance therapy for myeloma, there are studies of reduced dosing to mitigate the adverse effect on GvHD reported earlier; however, post-allo therapy with lenalidomide can remain challenging.[2] In contrast, a recent phase II study exploring bortezomib maintenance after tandem auto-allo in young and/or high-risk myeloma patients reported encouraging progression-free and overall survival, and lower rates of GvHD than in historic controls.[3] Whether a general improvement in GvHD management may potentially further improve the deliverability of post-allo therapy for pPCL is yet to be seen. Currently the uncertainty regarding GvHD and its putative impact on subsequent therapies, including emergent ones, is probably one of the main barriers to wider utilization of auto-allo transplants in pPCL and myeloma.[4]

Moving forward, the data from Lawless and colleagues will need to be viewed in the context of a rapidly evolving treatment landscape for myeloma and, potentially, pPCL. Therapy with the anti-CD38 monoclonal antibody daratumumab in an intensive combination demonstrated promising responses in pPCL in the OPTIMUM/MUKnine trial.[5] Chimeric antigen receptor T-cell therapies and drug conjugate monoclonal antibodies against B-cell maturation antigen have already received regulatory approval for myeloma,[6] and approvals for T-cell engager

monoclonal antibodies against multiple targets are pending.[7] However, the activity and safety of these approaches are still to be established in pPCL and, accordingly, more trials including pPCL patients are urgently needed. The SWOG-1211 and OPTIMUM/MUKnine trials, both of which enrolled pPCL and high-risk myeloma patients, are examples of the feasibility of such inclusive approaches.[8-10]

Until the necessary evidence emerges and the ability of novel immunotherapies to supersede transplantation in pPCL is proven, the work by Lawless *et al.* provides very useful information on the value of tandem auto-allo in pPCL, in particular for carefully selected, younger patients.

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