Double punch for plasma cell leukaemia

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

In this data-deprived context, the work by Lawless, Iacobelli and colleagues offers highly welcomed retrospective evidence from the EBMT registry, which has been providing invaluable insights for rare blood cancers like pPCL, long before ‘real-world data’ came into the focus of a wider audience. 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’) particularly focused on the impact of tandem over single transplants, but also comparison between the tandem approaches, which have not been studied at this detail in pPCL before.

Adjusting for baseline characteristics, auto-allo treated patients saw the best Progression Free Survival (PFS) risk reduction over single auto. Auto-auto showed a nominal, but non-significant improvement over single auto. Interestingly, modelling suggested patients in Complete Response (CR) after induction had longer PFS with auto-auto than auto-allo over single auto, and auto-allo the longest PFS in those not having achieved CR post-induction. Although risk for OS was nominally reduced for tandem approaches, it did not reach significance over single auto OS. Whilst the clinically non-acceptable high and early Non-Relapse Mortality (NRM) of single allo
was markedly lower with auto-allo, long-term OS 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 being often laterally adopted from myeloma practice. In this context, results from the current study are highly informative. The longer PFS for auto-allo, and in particular the reduced NRM 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 from auto-allo, highlighting the general need for post-transplant maintenance strategies. Two potentially interlinked questions emerge in context of maintenance: (1) would the advantage for auto-allo persist with maintenance? (2) would maintenance be feasible in context of acute and chronic GvHD post auto-allo?

Whilst it is impossible to answer (1) without further data, there is some myeloma-derived evidence regarding (2). For lenalidomide, the only approved maintenance therapy for myeloma, reduced dosing has been studied to mitigate the adverse effect on GvHD reported earlier; however, therapy with lenalidomide can remain challenging post-allo. In contrast, a recent phase 2 study exploring bortezomib maintenance post tandem auto-allo in young and/or high-risk myeloma patients reported encouraging PFS and OS, and lower rates of GvHD than in historic controls. Whether general improvement in GvHD management may potentially further improve deliverability of post-allo therapy for pPCL is to be seen – currently the uncertainty of GvHD and its putative impact on subsequent therapies, including emergent ones, is probably one of the main barriers to wider utilisation of auto-allo transplants in pPCL and myeloma.

Moving forward, the data by Lawless and colleagues will need to be seen in context of a rapidly evolving treatment landscape for myeloma and, potentially, pPCL. Therapy with the anti-CD38 monoclonal antibody (mAb) daratumumab in an intensive combination demonstrated promising responses in pPCL in the OPTIMUM/MUKnine trial. CAR-T cell therapies and drug conjugate mAbs against BCMA have already received regulatory approval for myeloma, and approvals for T-cell engager mAbs against multiple targets are pending. However, 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 for feasibility of such inclusive approaches.\textsuperscript{8-10}

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


