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Conditioning regimens for autologous haematopoietic stem cell transplantation – can NK cell therapy help?

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Transplant conditioning regimens are used to deliver dose intensive cytotoxic therapy prior to both autologous and allogeneic haematopoietic stem cell transplantation (HSCT), aimed at eliminating residual disease. For allogeneic transplantation they also provide immunological 'space' to facilitate engraftment. While allogeneic HSCT has witnessed sophisticated developments since the introduction of reduced intensity regimens, which now incorporate novel chemotherapy, monoclonal antibodies and immunomodulators, as well as graft manipulation, there has been relatively little change in the common regimens used in autologous HSCT over the last two to three decades.

Despite major advances in the biological treatments of myeloma and the lymphomas, autologous HSCT remains a cornerstone of treatment in both of these disease categories, which form the main indications for HSCT worldwide. High dose melphalan, originally developed in the 1980's (McElwain & Powles, 1983) remains the gold standard for myeloma care and the BEAM regimen (BCNU, Etoposide, Ara-C, Melphalan) (Linch et al, 1993) is still routinely used in both relapsed and resistant Hodgkin and non-Hodgkin lymphomas.

Despite more recent clinical trials attempting to challenge the standard high dose melphalan regimen in myeloma, there has been no widespread modification outside clinical trials, even in the setting of tandem transplantation (Maybury et al 2016). However, response duration following autologous HSCT in myeloma remains limited, and the desire for the longer remissions potentially achieved with allogeneic HSCT is counterbalanced by prohibitive treatment-related mortality. There is thus considerable room for improvement.

NK cells represent an important arm of the innate immune system and have well-defined roles in mediating immunity against viruses and cancer. Prior exposure or sensitization is not needed for NK cells to kill their target. Instead activation of the Killer Immunoglobulin-like Receptor (KIR) in the absence of HLA class I molecules on target cells is thought to trigger cytolysis (reviewed in Ullah et al 2016). In the setting of T cell depleted haploidentical stem cell transplant, donor NK cells have been demonstrated to mediate potent anti-leukaemic effects (Ruggeri et al 2002, Ruggeri et al 2007). This effect is most dominant against myeloid malignancies when mismatching in donor and recipient KIR and allo-reactive NK cells are present (Ruggeri et al 2007). In addition, donor NK cells can eliminate HLA-mismatched recipient haematopoietic cells after transplant (Ruggeri et al 2002) and can thus, theoretically, be harnessed as cytotoxic mediators against malignant cells residing in the bone marrow. Whether beneficial effects can be mediated against plasma cell malignancies remains untested at this point.

In this issue of the BJH, Shah et al (2016) have taken the step of modifying the standard melphalan 200mg/m^2 regimen used in autologous HSCT for myeloma in two aspects. Firstly, they have added the widely used anti-myeloma drug, lenalidomide, which is known to synergize with alkylators, such as melphalan. Secondly they have incorporated infusions of massively expanded, GMP-grade umbilical cord derived NK cells from HLA-mismatched donors. These NK cells putatively undergo enhanced activation by lenalidomide in vivo. Finally, the

lymphodepletion invoked by high dose melphalan provides space for homeostatic expansion of infused NK cells early after HSCT.

Initial results of the study of Shah et al merely support the safety of this approach, and in particular, an absence of GVHD. There is also evidence presented that circulating NK cells can survive for up to 26 days. Whether this short-term persistence, along with the activating effect of lenalidomide, is sufficient for NK cells to exert a clinically beneficial anti-tumour effect beyond that expected by the standard melphalan-conditioned autologous HSCT now requires adequately powered prospective studies. Given the approach and potential for activated HLA-disparate NK cells to mediate responses against mismatched hematopoietic stem cells, effects on engraftment will need to be assessed in an ongoing fashion.

Cord blood is now a widely collected source of donor haematopoietic cells and registries can provide rapid access to appropriate HLA matching services. Although cord blood banks are primarily established to supply complete units for transplantation, recent trends dictated by the ease of use of haploidentical family donors as alternative graft sources (reviewed in Kekre & Antin, 2016) may mean that cord blood will be increasingly valuable as a source for cell therapies.

Clearly, if evidence accrues that combining chemotherapy regimens with NK and/or other cellular therapy improves clinical outcomes, then there may be widespread implications for many types of cancer. Nonetheless, delivery of these cell therapies is inevitably complex, with considerable technical, financial and regulatory implications. However, just as reduced-intensity conditioning transformed allogeneic HSCT into a ‘platform for cellular immunotherapy’, it is possible that new approaches to autologous HSCT that incorporate cellular therapies may eventually build on standard practice to improve outcomes.

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