Stem cell transplantation – GvHD - Section 2

GvHD prophylaxis with cyclophosphamide post transplant

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Our group has developed the use of high-dose post-transplantation cyclophosphamide (PTCy) to selectively remove alloreactive T cells without compromising engraftment.[1] This protocol has allowed for successful transplantation of HLA-haploidentical (haplo) grafts, thus expanding the donor pool for the many patients who would not otherwise be a candidate for this life-saving procedure.[2] Two parallel prospective BMT Clinical Trials Network (CTN) studies assessed non-myeloablative conditioning (NMA) with PTCy–haploBMT or umbilical cord blood transplantation (UCBT). After a median follow-up duration of 1-year, almost all parameters (engraftment, grade III–IV acute GvHD, chronic GvHD, NRM and grade 3–4 toxicities) favoured PTCy–haploBMT; however, the relapse rate was lower after UCBT, leading to similar PFS between the two cohorts.[3] Longer-term follow-up data showed similar trends for 3-year outcomes between UCBT and PTCy–haploBMT (NRM 28% *versus* 8%, relapse 36% *versus* 58%, PFS 36% *versus* 35%, overall survival 39% *versus* 54% for UCBT and haploBMT, respectively. UCB and PTCy–haploBMT are currently being compared in an ongoing randomized phase III trial (NCT01597778). Several other centers rapidly adopted PTCy and made various modifications to the original protocol such as increasing the intensity of conditioning or substituting peripheral blood stem cells (PBSCs) for bone marrow as the graft source. These developments were driven in part by concerns that the original NMA conditioning was insufficient to control aggressive hematologic malignancies, and that use of PBSCs may provide ease of protocol acceptance in centres where this graft source is preferred, as well as to decrease the rejection rate due to higher donor T cell dose in comparison to BM.[4-6] We have also shown that after myeloablative conditioning and HLA-matched-related or HLA-matched-unrelated bone-marrow transplantation, PTCy can be effective as single-agent GVHD prophylaxis.[7-9] This strategy is currently being compared with TCD and calcineurin-inhibitor-based GVHD prophylaxis in a three arm randomized phase III study (NCT02345850). Over the last couple of years, a growing body of literature has emerged from multiple groups in the United States and Europe indicating that haplo BMT using PTCy results in outcomes on par with those using HLA matched donors. Recent comparisons of BMT outcomes for acute myeloid leukemia and lymphomas showed equivalent survival but less acute and chronic GvHD for haplos with PTCy compared with MUD allografts.[10,11] From the biological perspective, the approach is based on mouse models of MHC-mismatched alloBMT and the studies showing that hematopoietic stem cells express high levels of aldehyde dehydrogenase which confers cellular resistance to cyclophosphamide.[2] These pre-clinical studies are now being extended with a goal to decipher the immunologic effects of PTCy on T cell subsets and overall immune dynamics.[12,13]

References

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