How we perform haploidentical stem cell transplantation with post-transplant cyclophosphamide

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Clinical case

- A 58-year-old KURDISH man with insulin-dependent diabetes, hypertension, was diagnosed with AML with a complex karyotype after presenting with leukocytosis, anemia, and thrombocytopenia.
- He underwent initial manage-ment with fluids, hydroxyurea, and allopurinol, then initiation of induction chemotherapy with cytarabine and daunorubicin
- His clinical course was complicated by neutropenic fever that resolved with cefepime.
- A day 14 BM biopsy showed no residual AML.
- On his recovery bone marrow biopsy, he achieved a morphologic complete remission (CR), but with residual cyto-genetic abnormalities.

Clinical case

- At the time of count recovery, he was referred for discussion of HSCT.
- His HSCT-specific comorbidity index score was 2.
- The patient’s immediate family included an 88-year-old father, an 85-year-old mother, 2 brothers aged 60 and 52 years old, and 1 sister who was 65 years old.
- He did not have any biological children.
- Both parents shared one HLA haplotype with the patient; the younger brother and his sister also shared one HLA haplotype; and the older brother was disparate .
- Class I and class II screens for DSA were negative.
- A preliminary unrelated donor search showed 3 potential donors who had a low probability of being a 10/10 HLA match.

Questions

- Is there benefit in waiting for a completed matched unrelated donor search vs proceeding directly with a haploidentical donor?

Questions

- Does conditioning intensity matter?

Questions

- Does graft source matter?

Questions

- Do DSA matter?

Questions

- Do MRD and active disease matter?

Clinical case continued

- The patient received 1 cycle of high-dose cytarabine consolidation that was uncomplicated.
- His pre-transplant BM showed CR without MRD.
- Sixty days from the start of consolidation, he began conditioning consisting of fludar-abine, cyclophosphamide, ATG followed by haploidentical peripheral BM graft with a total nucleated cell count of 2.9 * 107 total nucleated cells per kilogram from his brother, the donor.
- Post grafting GVHD prophylaxis included PTCy on days 3 and 4, followed on day 5 by initiation of MMF and tacrolimus.

Clinical case continued

- He tolerated the procedure well, with his main complication being high fevers with hemodynamic stability from the time of graft infusion until after completion of PTCy on day 4, which was attributed to cytokine release syndrome (CRS) secondary to the HLA mismatches between donor and recipient.
- He had nausea and diarrhea during the first month.
- Neutrophil engraftment occurred on day 15, with platelet recovery occurring on day 19.

Clinical case continued

- The MMF was discontinued on day 35, and the patient's gastrointestinal symptoms resolved shortly thereafter.
- He developed grade 1 overall acute GVHD after tacrolimus was discontinued on day 180 that improved with topical steroids.
- Days 90 and 180 BM biopsies showed remission with normal cytogenetics and 100% donor engraftment in both CD31 and CD331 cells.

Questions continued

- How common is CRS after haploidentical graft infusion, and how is it treated?

Questions

- How long do we continue post grafting immunosuppression?

Clinical case continued

- At 8 months after HSCT, our patient had 100% donor chimerism in the peripheral blood and BM, but he developed isolated testicular relapse that was treated with surgery, radiation, and prophylactic intrathecal chemotherapy.
- At 13 months after HSCT, he developed systemic relapse, with BM biopsy revealing 63% myeloblasts with 49% recipient DNA.
- Karyotype analysis at the time of relapse showed a complex karyotype.
- Further molecular studies confirmed HLA loss.

Clinical case continued

- The patient underwent salvage chemotherapy with mitoxantrone, etoposide, and cytarabine and achieved a second CR with MRD negativity by flow cytometry.
- During salvage chemotherapy, we inquired regarding the availability of second-degree relatives.
- The patient underwent a second fludarabine/cyclophosphamide haplo-PBSCT PTCy using a niece with a haplotype mismatch distinct from the original donor and received MMF and sirolimus prophylaxis.

Clinical case continued

- He experienced stage III aGVHD of the skin only, overall grade II aGVHD, that required systemic steroids started on day 65 posttransplant. Steroids were successfully tapered after 3 months, and sirolimus was stopped 1 month after steroid discontinuation. He was alive and in remission at last follow-up, approximately 14 months after HSCT.

Questions

- How do we treat relapse after haplo-HSCT?

Questions

- What are the unique aspects of relapse after
- haplo-HSCT?

Conclusions

- Haplo-HSCT with PTCy is an increasingly used platform, given its advantages of rapid identification of donors, low cost relative to other alternative donor strategies, simplicity of applying PTCy clinically, and comparability to HLA-matched HSCT.
- One of the most complex issues with haplo-HSCT is donor selection, given that multiple haploidentical donors are often available for a given recipient.

Conclusions

- A significant barrier to haplo-HSCT is the high incidence of DSA in parous females, which can preclude familial haploidentical donors.
- Finally, as with all HSCT, relapse remains the biggest barrier to successful haplo-HSCT and novel strategies to reduce relapse should be the focus of future investigation.