TREATMENT OF RECURRENT PEDIATRIC MYELODYSPLASTIC SYNDROME POST HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction

Survival is dismal for the 40-60% of children with MDS who relapse post allogeneic HCT[1,2,3]. Strategies to decrease relapse risk include use of cytoreduction prior to HCT or maintenance treatment after HCT, data on the utility of these approaches remains limited[4-12]. Rapid withdrawal of immune suppression or use of donor lymphocyte infusion (DLI) can enhance the graft versus leukemia effect and achieve disease control in some cases[13,14]. Addition of hypomethylating agents to DLI may provide additional benefit[15] and second HCT should be considered[16-21]. While several novel therapies may alter the future landscape of MDS therapy[22-28] (Table 1), the optimal approach to relapsed pediatric MDS remains unclear. We report the management of a child who relapsed less than 70 days after initial HCT. Our approach demonstrates that multimodal therapy may permit prolonged survival with excellent quality of life (QOL) despite lack of long-term cure.

Results

A previously healthy 4-year-old girl presented with fever. Physical exam at presentation was normal; laboratory studies demonstrated a white blood cell count of 3820 cells/μL with 6% circulating blasts, absolute neutrophil count 640 cells/μL, hemoglobin 11.5 g/dL and platelets 74,000 cells/μL. Bone marrow (BM) testing was diagnostic for MDS with excess blasts-2 (Figure 1). Next generation sequencing panel showed PTPN11 p.A72V, 32% of 1331 reads and WT1 p.S382-frameshift, 17% of 848 reads. Fluorescence in situ hybridization (FISH) detected monosomy 7. An underlying germline disorder, which is present in at least 30% of pediatric MDS cases[3], was not identified. Extensive testing included telomere lengths, chromosome breakage, pancreas iso-amylase and whole exome sequencing.

She received decitabine (20 mg/m^2 for 10 days); follow-up BM evaluation demonstrated a reduction in blasts to 3% with persistent multilineage dysplasia (Figure 2A, B). She proceeded to HCT conditioned with myeloablative busulfan and cyclophosphamide followed by BM graft from her 10/10 HLA matched father (5.84x10^{6}CD34+ cell/kg) (Figure 2C). Graft versus host disease (GvHD) prophylaxis included cyclosporine and methotrexate. Engraftment occurred on day 28 and she experienced minimal transplant associated toxicities and no GvHD. BM evaluation on day 30 was without evidence of MDS. However, surveillance BM on day 60 (7 months post diagnosis) demonstrated recurrent disease (Figure 2B). Cyclosporine was rapidly weaned followed by treatment with azacytidine (75 mg/m^2 for 7 days) and DLI (1 x 10^6 CD3+ T cells/kg). Salvage treatment with azacytidine in combination with fludarabine / cytarabine / granulocyte- growth-

factor led to a measurable residual disease (MRD) negative remission. Maintenance therapy was initiated with azacytidine (75mg/m^2 for 7 days, 28-day cycles) and DLI every other cycle (3 x 10^6 CD3+ T cells/kg for cycle 1, 2 x 10^7 CD3+ T cells/kg for cycle 3). Remission was maintained for 4 cycles, until she developed bone pain and recurrent cytopenia. A BM evaluation demonstrated second recurrence of MDS (17 months post diagnosis). She received venetoclax (14mg/kg, 800 mg adult equivalent) combined with cytarabine (1000 mg/m^2 IV every 12 hours for 5 days). BM performed on day 22 of treatment was acellular and venetoclax was held. Repeat BM assessment on day 42 showed remission by flow cytometry and the patient proceeded to second HCT using a 10/10 HLA matched unrelated donor (2.75 x 10^6CD34+ cells/kg) after fludarabine, clofarabine and busulfan conditioning. Engraftment occurred on day 16. The second HCT was uncomplicated; CD34 chimerism was 100% donor 2 on day 30 and cyclosporine was weaned by 186 days post HCT. She remained disease-free until one year post second transplant when routine surveillance demonstrated 70% peripheral blasts consistent with transformation to AML/MDS (˜32 months after diagnosis). Re-induction with cytarabine and fludarabine resulted in MRD negative remission. An experimental cellular therapy did not mediate a durable remission. She relapsed for a fourth time with a significant blast burden (MDS/AML) and received CPX-351 with the goal to achieve disease control prior to a planned investigational 3rd HCT. Her disease was refractory to this re-induction attempt and treatment goals were transitioned to palliative approaches.

Discussion

Disease relapse remains the leading cause of mortality for children undergoing HCT for MDS. Treatment options for those who recur early post HCT are limited, and cure is unlikely. Despite the high risk of mortality, a second HCT can achieve long-term survival in well-selected patients[16,17,19-21]. In a retrospective analysis of pediatric patients with acute leukemia and MDS who received a second HCT the single predictor for long term survival was disease control at time of HCT[16].

We report a pediatric patient who received multimodal therapy for recurrent MDS. Given the proximity of her first recurrence to initial HCT, a second HCT was initially not felt to be a therapeutic option given concern for disease refractoriness and risk of treatment related mortality (TRM). Treatment with azacytidine and DLI followed by a myelosuppressive reinduction achieved a second remission until about 12 months from first HCT, at which point she was felt to be a suitable second transplant candidate. Though there is limited evidence for using an alternative donor for a second HCT[16] we chose an unrelated fully matched donor to facilitate graft versus leukemia effect[18]. While ultimately her disease was incurable, the therapies utilized from time of initial recurrence onward afforded her excellent QOL for 2.5 years - most of her time was spent outpatient with a high-performance score (Figure 2C).

Low disease burden at the time of HCT for MDS has been associated with improved outcome[6,21], however cytoreductive treatment prior to HCT is associated with inferior outcome[5,29]making the role of chemotherapy prior to HCT in pediatric MDS highly controversial. With the increasing utilization of novel targeted therapeutics in pediatric MDS, we may discover that the advantages of lower disease burden due to cytoreduction outweigh the possible toxicities. The combination of a hypomethylating agent or cytarabine with the Bcl-2 inhibitor venetoclax has been well tolerated in pediatric myeloid disease and is equally efficacious to conventional chemotherapy in adult MDS[30-33]. Novel therapeutic approaches include enhancement of GVL effect by checkpoint inhibition but risk of GvHD remains a major concern[27,34]. While cure of pediatric MDS recurring early post HCT remains unlikely, novel treatment approaches should be considered. We utilized multiple therapeutic approaches, including second HCT, DLI, maintenance chemotherapy and experimental cellular treatments towards the goal of minimizing toxicity and maximizing QOL while still striving for cure. Investigational approaches in pediatric MDS should be considered (Table 1)[7-9,11,35-37]. The role of a third HCT in relapsed MDS is controversial given the risk of toxicity and should be done within the context of a clinical trial.

Conclusion

For children with relapsed MDS with a good performance status and absence of uncontrolled infections,

GvHD, and other treatment related toxicities, a second HCT should be considered if disease control can be achieved and if aligned with the family's goals. Acknowledging that early second HCT is associated with increased TRM[16,18,21], temporizing disease control with less myelosuppressive agents, like hypomethylating agents in tandem with DLI, may be beneficial. Individualized treatment approaches that utilize targeted therapies with less risk for TRM like Bcl-2 inhibition (e.g.venetoclax)[38] or immunotherapy (e.g. magrolimab) should be further studied in pediatric MDS. Consolidation strategies in the event of relapse after second HCT are not standardized; selected novel treatments might provide therapeutic benefit with minimal toxicity and therefore warrant consideration.

Conflict of Interest statement

FW, YP, JB, MK, SB, JR, AS, JW, LL, JH declare no relevant conflict of interest. AEP has received research funding from AbbVie, Inc. SP receives support for the conduct of clinical trials through Boston Children's Hospital from AlloVir, Atara, and Jasper, SP provides consulting (CellEvolve, Pierre Fabre) and receives honoraria from Regeneron, SP is an Inventor related to development of third party viral specific T cells program with all rights assigned to Memorial Sloan Kettering Cancer Center. JAP receives support for the conduct of clinical trials through Boston Children's Hospital / Dana-Farber Cancer Institute from AbbVie, Ymab Therapeutics and Servier and is on the advisory board for foresee pharmaceuticals.

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Figure 1: Myelodysplastic syndrome with excessive blasts.

A) Histology of bone marrow biopsy core (H&E) showing dysplastic megakaryocytes and 10-15% aberrant blasts. B) Bone marrow aspirate (Wright-Giemsa) with dysplastic micro-megakaryocytes, erythroid with nuclear irregularities, and hypo-granular myeloids. C) Karyotype from the time of initial diagnosis, with monosomy 7 detected in 61% cells by FISH. D) Flow cytometry detected 13% myeloid blasts expressing CD13, CD33, CD34, CD117, CD11b, MPO and HLA-DR.

Figure 2: Timeline of disease management and response to treatment.

A) Overview of the disease status over time. B) Graph showing disease characteristics over time. Monosomy 7 was measured by FISH. CD34 donor chimerism for donor 1 and donor 2 were measured by next generation sequencing at the American Red Cross. Multi-parameter flow cytometry performed at Boston Children's Hospital was used to measure aberrant blast percentage. AML MRD flow cytometry represents testing done at Hematologics, Inc., Seattle, WA. Lower panel zoomed to improve MRD visualization. C) Overview of treatment over time, inpatient time is highlighted. Immunosuppressive therapy (IST), Donor Lymphocyte infusions (DLI), Fludarabine, Cytarabine and Granulocyte colony-stimulating factor (FLAG).

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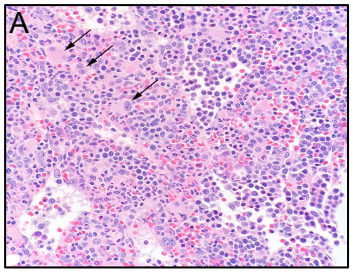
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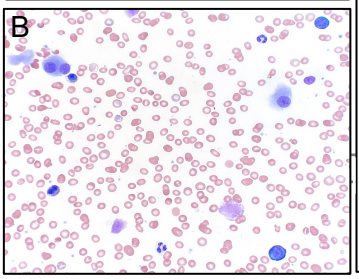
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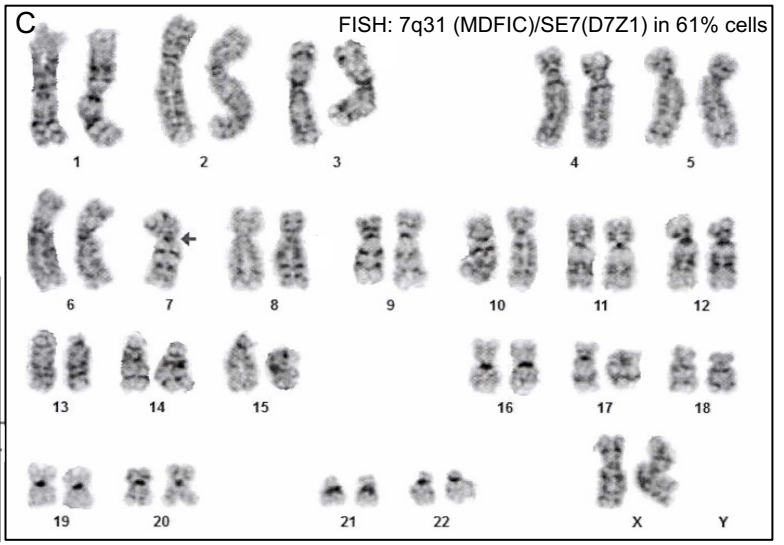
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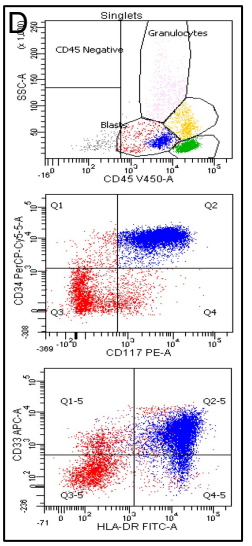
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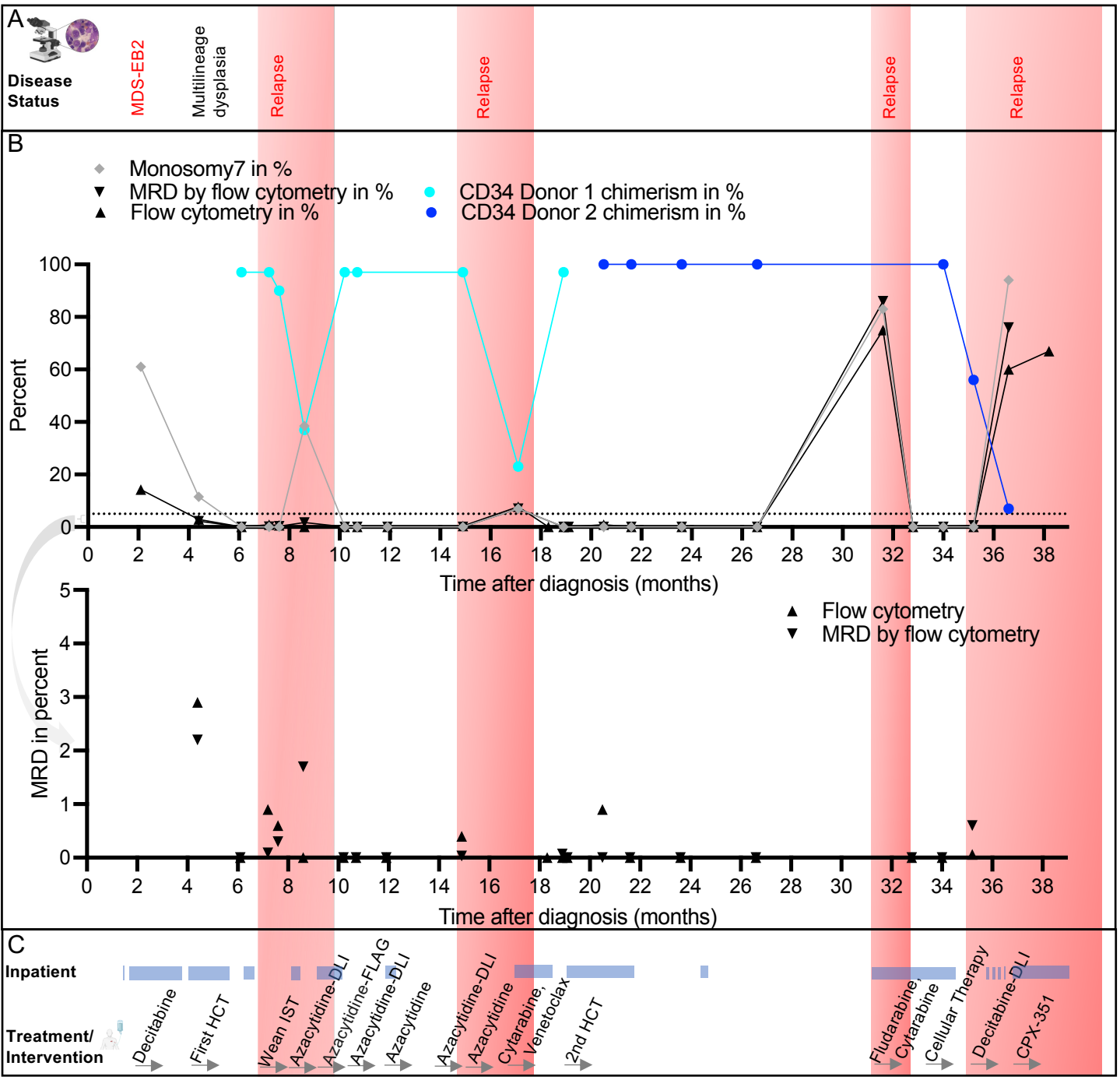
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Disease Status
MDS-EB2
Multilineage dysplasia
Relapse
Relapse
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B
Monosomy7 in %
MRD by flow cytometry in %
Flow cytometry in %
CD34 Donor 1 chimerism in %
CD34 Donor 2 chimerism in %
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Time after diagnosis (months)
Flow cytometry
MRD by flow cytometry
MRD in percent
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C
Inpatient
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Decitabine
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