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CASE REPORT

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Treatment of recurrent pediatric myelodysplastic syndrome post hematopoietic stem cell transplantation

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Key Clinical Message

Treatment of recurrent myelodysplastic syndrome (MDS) after hematopoietic cell transplantation (HCT) remains challenging. We present a 4-year-old girl experiencing early MDS relapse post-HCT treated with a multimodal strategy encompassing a second HCT and innovative targeted therapies. We underscore the potential of a comprehensive treatment approach in managing recurrent pediatric MDS.

KEYWORDS

disease control, hematopoietic stem cell transplantation, myelodysplastic syndromes, relapse

1 | INTRODUCTION

Survival is dismal for the 40%–60% of children with myelodysplastic syndrome (MDS) who relapse post allogeneic hematopoietic cell transplantation (HCT).[1–3] Strategies to decrease relapse risk includes 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

TABLE 1 Novel therapeutic approaches for pediatric AML/MDS.

Mechanistic categories	Example	Selected references/clinical trial numbers (as of 05/02/2023)
Hematopoietic stem cell transplant approaches	-KIR-favorable donor selection	Mehta, Rezvani 2016; Davies, Iannone et al. 2020
	-Selective graft depletion strategies	Mamcarz, Madden et al. 2020 NCT00566696 - completed
	-Expanded cord trial	NCT04990323
	-Uproleselan with pre-transplant conditioning[a]	NCT05569512
	-Maintenance therapy after HCT with decitabine and G-CSF	NCT05796570
	-Preemptive donor-derived ex-vivo expanded NK-cells	NCT04836390
Cellular therapies	-CD33 CAR T cell therapy	NCT03971799, NCT05105152
	-CD123 CAR T cell therapy	NCT04318678, NCT04678336
	-Cytokine-induced memory-like NK cell therapy	NCT04024761
	-Cytokine-induced memory-like NK-cell + DLI	NCT03068819
	-CLL-1 CAR-T cell therapy	NCT04219163
Antibody drug conjugate	-CD33 directed treatment with fractionated gemtuzumab	Debureaux, Labopin et al. 2020
	-CD123 directed treatment with tagraxofusp / IMGN632	Lane 2020
Immunotherapies	-Decitabine plus ipilimumab	Garcia, Flamand et al. 2020
	-Azacytidine plus nivolumab	NCT03825367
	-Magrolimab	NCT03248479
	-CD38 directed treatment with daratumomab	NCT03067571 - completed
Novel small molecule therapies	-Azacytidine, venetoclax, and trametinib (RAS mutation)	NCT04487106 - completed
	-Venetoclax plus selinexor	NCT04898894
	-Lenalidomide (Monosomy7 or 5q-)	Adema, Kerr et al. 2019

Abbreviations: CAR, chimeric antigen receptor; KIR, killer immunoglobulin-like receptor; G-CSF, granulocyte-colony stimulating factor; HCT, Hematopoietic stem cell transplant; NK, Natural Killer.

[a]MDS not included.

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.

2 | 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 (5.84 x 10^6 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

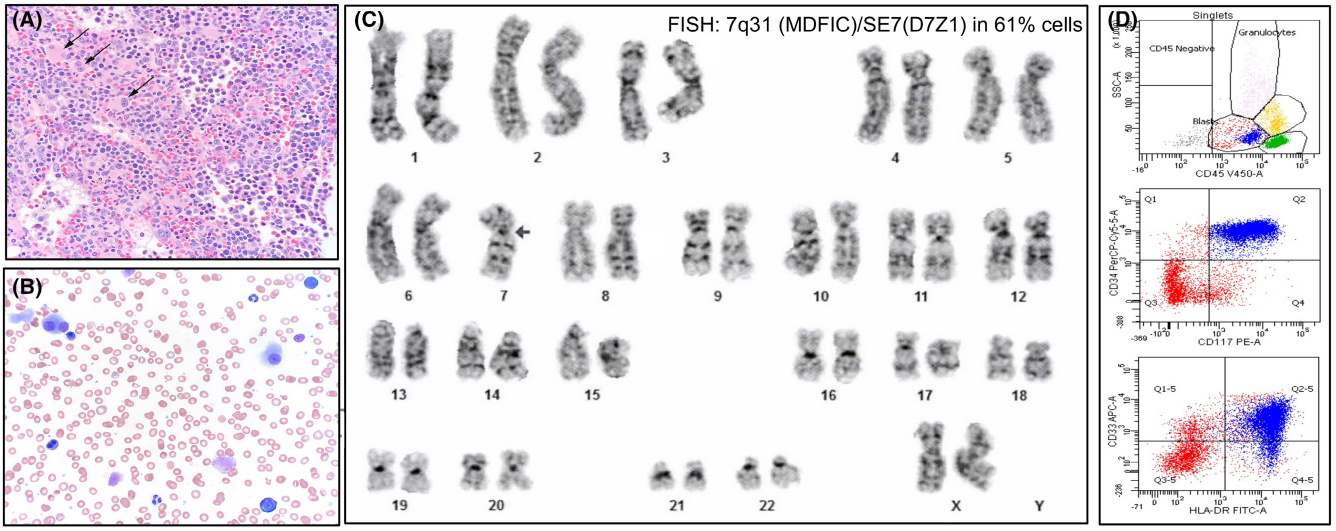

FIGURE 1 Myelodysplastic syndrome with excessive blasts. (A) Histology of bone marrow biopsy core (H&E) showing dysplastic megakaryocytes and 10%–15% aberrant blasts. (B) Bone marrow aspirate (Wright-Giemsa) with dysplastic micro-megakaryocytes, erythroid with nuclear irregularities, and hypo-granular 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.

to a measurable residual disease (MRD) negative remission. Maintenance therapy was initiated with azacytidine (75 mg/m^2 for 7 days, 28-day cycles) and DLI every other cycle (3×10^6 CD3+ T cells/kg for cycle 1, 2×10^7 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 (14 mg/kg, 800 mg adult equivalent) combined with cytarabine (1000 mg/m^2 IV every 12 h for 5 days). BM performed on day 22 of treatment was acellular and venetoclax was held. Repeat BM assessment on day 42 showed MRD negative remission by flow cytometry and the patient proceeded to second HCT using a 10/10 HLA matched unrelated donor (2.75×10^6 CD34+ 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 1 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.

3 | 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

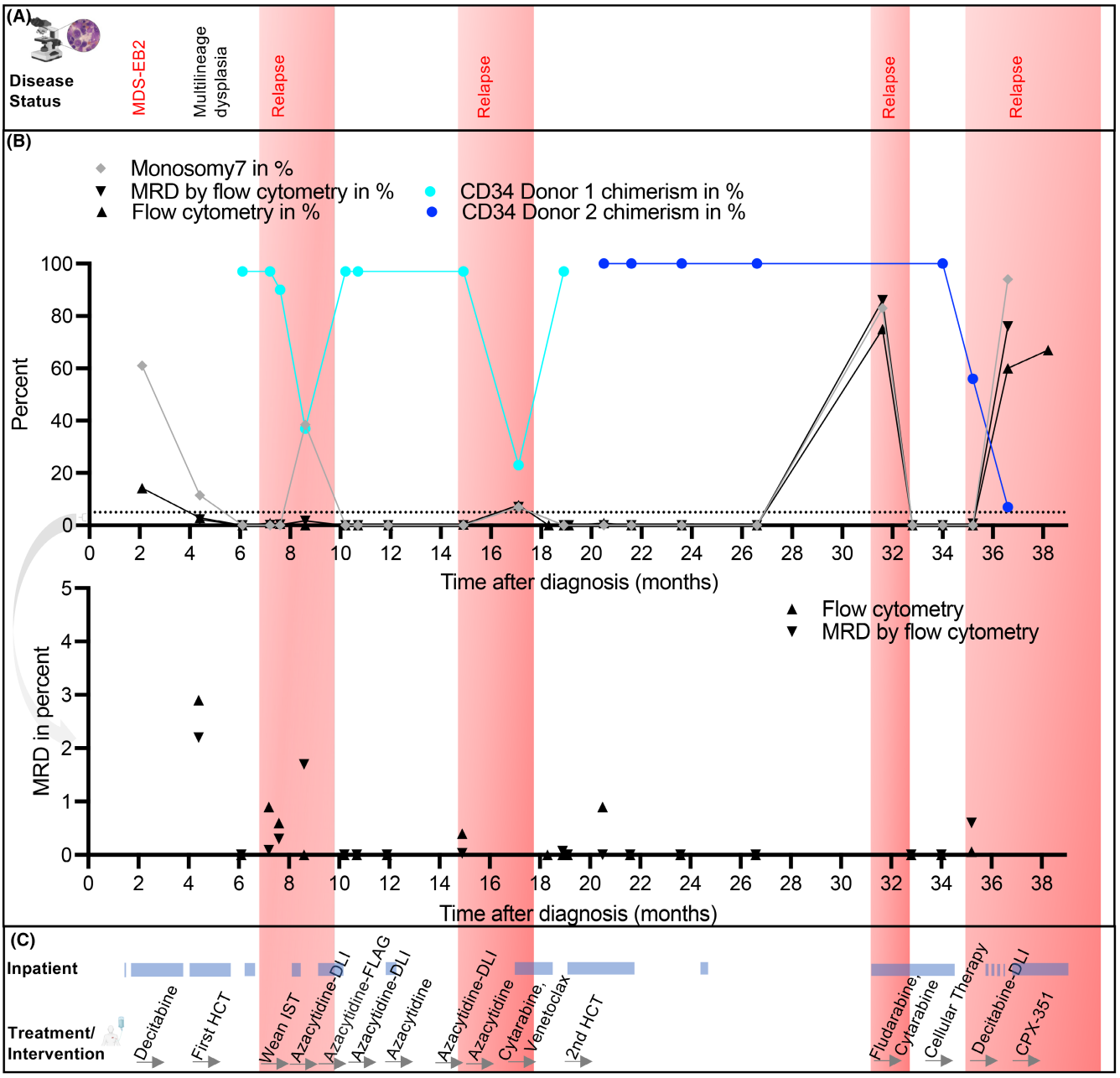

FIGURE 2 Timeline of disease management and response to treatment. (A) Overview of the disease status over time. (B) Graph showing disease characteristics over time. Monosomy 7 was measured by FISH. CD34 donor chimerism for donor 1 and donor 2 were measured by next generation sequencing at the American 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).

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.

4 | 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)[11] 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.

AUTHOR CONTRIBUTIONS

Franziska Wachter: Conceptualization; funding acquisition; writing – original draft; writing – review and editing. **Yana Pikman:** Conceptualization; supervision; writing – review and editing. **Jacob Bledsoe:** Data curation; writing – review and editing. **Malika Kapadia:** Writing – review and editing. **Susanne Baumeister:** Data curation; supervision; writing – review and editing. **Jared Rowe:** Writing – review and editing. **Akiko Shimamura:** Writing – review and editing. **Andrew E. Place:** Writing – review and editing. **Susan Prockop:** Supervision; writing – review and editing. **Jennifer Whangbo:** Writing – review and editing. **Leslie Lehmann:** Supervision; writing – review and editing. **John Horan:** Writing – review and editing. **Jessica Pollard:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Franziska Wachter, Yana Pikman, Jacob Bledsoe, Malika Kapadia, Susanne Baumeister, Jared Rowe, Akiko Shimamura, Jennifer Whangbo, Leslie Lehmann, John Horan declare no relevant conflict of interest. Andrew E. Place has received research funding from AbbVie, Inc. Susan Prockop receives support for the conduct of clinical trials through Boston Children's Hospital from AlloVir, Atara, and Jasper, Susan Prockop provides consulting (CellEvolve, Pierre Fabre) and receives honoraria from Regeneron, Susan Prockop 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the parent to publish this report in accordance with the journal's patient consent policy. This case report is IRB exempt per institutional guidelines.

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