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Phase II Study of Allogeneic Hematopoietic Stem Cell Transplantation for Children with High-Risk Neuroblastoma Using a Reduced-Intensity Conditioning Regimen: Results from the AIEOP Trial

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A B S T R A C T

Despite aggressive multimodal treatment, the outcomes of pediatric patients with high-risk (HR) neuroblastoma (NB) remain poor. The rationale for allogeneic hematopoietic stem cell transplantation (allo-HCT) to treat NB was based on the possible graft-versus-tumor effect; however, toxicity limits its efficacy. We sought to prospectively assess the feasibility and efficacy of allo-HCT using a reduced-intensity conditioning regimen in pediatric patients with HR NB in a multicenter phase II trial. Primary endpoints were the rate of neutrophil and platelet engraftment, 5-year transplantation-related mortality (TRM), and disease-free survival (DFS). Secondary endpoint measures included the incidence of acute graft-versus-host disease (aGVHD) and chronic GVHD. Fifty-one patients were enrolled in the study. The 5-year cumulative incidence (CuI) of TRM was 29.4 ± 6.4%, and that of DFS was 11.8 ± 4.5%. Patients undergoing allo-HCT within 1 year of diagnosis or with bone marrow as their stem cell source had a higher DFS probability. The CuI of neutrophil engraftment, platelet engraftment, and grade II-IV aGVHD was 97.9 ± 2.1%, 93.8 ± 3.5%, and 47.1 ± 7.0%, respectively. The development of new therapeutic strategies could further improve disease control.

INTRODUCTION

Neuroblastoma (NB) is the most frequently occurring extracranial pediatric tumor and the most common solid tumor in children age <5 years [1]. Patients with high-risk (HR) disease, most of whom have metastatic disease at presentation, are particularly challenging [2–5]. Current multimodal protocols for HR NB include multiagent chemotherapy, surgical resection of the primary site, autologous hematopoietic stem cell transplantation (auto-HCT), and radiotherapy [6]. In a large retrospective study by the Children's Oncology Group, HR NB patients had a 5-year event-free survival (EFS) rate of 50.8% [7]. Outcomes are even worse for patients relapsing after first-line treatment or failing to respond, with a 4-year overall survival (OS) rate of 20% [4].

Auto-HCT is currently used as consolidation therapy for HR patients, offering improved disease-free survival (DFS) compared to standard chemotherapy [8,9]. Consolidation with tandem auto-HCT has shown even more favorable outcomes, with a 3-year EFS rate of 61.6% [10]. The recent introduction of immunotherapy targeting GD2 with monoclonal antibodies and development of new strategies, such as chimeric antigen receptor T cell therapy, for relapsed or refractory NB have shown promising outcomes [11]. However, long-term results of HR NB remain unsatisfactory, with disease recurrence occurring in a considerable proportion of patients [3,12,13].

Allogeneic HCT (allo-HCT) has been proposed as an alternative to auto-HCT for treating HR NB, although the latter shows a trend toward improved survival, albeit without statistical significance [14]. A retrospective study from the Japanese Neuroblastoma Research Group showed that in patients with HR NB, allo-HCT was predictive of better EFS, although the prognosis remained poor [15]. A retrospective analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) reported the outcomes of HR and refractory NB patients receiving allo-HCT, showing superior EFS for those who did not undergo a previous auto-HCT [16]. Transplantation-related mortality (TRM) represents a limitation to the applicability of the procedure, however [16]. We sought to determine the effectiveness of allo-HCT with reduced-intensity conditioning (RIC) in children with HR NB and an available HLA-matched related or unrelated donor on a prospective, multicenter phase II trial conducted by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).

METHODS

Study Design

This prospective, nonrandomized multicenter phase II study designed by the AIEOP working group on NB and HCT was conducted among 15 Italian centers. Details of each participating center are provided in Supplementary Data. The study protocol was approved by the Ethics Committee of each center (study code 85/2005/O), and the trial was performed in accordance with the Declaration of Helsinki principles. Written informed consent was provided by each patient's legal guardian.

Patients

Eligible patients were those age ≤18 years at initial diagnosis with HR NB, defined as International Neuroblastoma Risk Group Staging System (INRGSS) [7,17] stage M NB, and those with INRGSS stage L1-L2 with *MYCN* amplification. Patients with HR NB were scheduled to receive allogeneic allo-HCT as consolidation after completing the initial multimodal protocol. Patients defined as non-HR at diagnosis who were nonresponsive to first-line treatments or presented with local and/or metastatic relapse at >6 months from auto-HCT were eligible. Additionally, patients diagnosed with HR NB who were refractory to treatment or experienced relapse were eligible for inclusion. Exclusion criteria included the presence of disease progression, severe organ dysfunction, life expectancy of <6 months, Karnofsky Performance Status <60, and refusal of consent for the study.

Procedures

Patients were scheduled to receive allo-HCT from a matched family donor (MFD) or a 9/10 or 10/10 matched unrelated donor (MUD) using either peripheral blood stem cell (PBSC) or bone marrow (BM) grafts. The conditioning regimen consisted of thiotepa at 15 mg/kg in 2 daily doses on days -4 and -3 and melphalan at 140 mg/m^2 on day -1. Graft-versus-host disease (GVHD) prophylaxis was chosen based on donor type and stem cell source. GVHD prophylaxis for MFD allo-HCT consisted of cyclosporine A (CsA) administered at 2 mg/kg from day -4, and that for MUD allo-HCT consisted of CsA at 2 mg/kg from day -4, methotrexate (10 mg/m^2 on day +1 and 8 mg/m^2 on days +3, +6, and +11), and antithymocyte globulin (ATG; Genzyme) at 2.5 mg/kg from day -4 to day -2. CsA tapering was started on day +45 and interrupted on day +90 in the absence of signs of GVHD.

Outcomes

Primary outcome measures were the cumulative incidence (CuI) of neutrophil and platelet engraftment and 5-year TRM and DFS. Secondary outcome measures included acute GVHD (aGVHD) and chronic GVHD (cGVHD).

Statistical Analysis and Definitions

DFS was defined as the probability of being alive and free from disease at a specific time point after HCT. DFS was calculated using Kaplan-Meier method and reported as probability and standard deviation (SD) starting from the day of stem cell infusion. TRM was defined as death from any cause in the first 100 days after HCT or death without evidence of disease progression/relapse at any time point. TRM was calculated using CuI to adjust the analysis for competing risks; relapse was considered a competing risk and reported at 100 days, 1 year and 5 years after allo-HCT. Differences in DFS were evaluated by the log-rank test, and differences in CuI were evaluated by Grey's test. A P value $< .05$ was considered statistically significant in all analyses. The Wilcoxon rank-sum test and Fisher exact test were used to compare continuous and categorical clinical variables. SPSS 24.0.0 for Windows (IBM) was used for statistical analyses. aGVHD and cGVHD were diagnosed and graded according to the Glucksberg criteria [18]. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $\geq .5 \times 10^9$/L. Platelet engraftment was defined as independence from platelet transfusion for at least 7 days with a platelet count $>20 \times 10^9$/L.

RESULTS

Patient Characteristics

The study cohort comprised 51 patients who underwent allo-HCT at 15 Italian centers within the AIEOP network between 2005 and 2015. According to the inclusion criteria, 5 patients (9.8%) were included for HR disease without relapse or refractoriness to initial therapy, 35 patients (68.6%) for HR disease with relapse occurring at least 6 months after auto-HCT, 9 patients (17.6%) for HR disease refractory to initial therapy, and 2 patients (3.9%) for non-HR disease with relapse occurring at least 6 months after auto-HCT. Patients received first-line treatment according to the HR-NBL-1.7/SIOPEN protocol and its subsequent amendments. Forty-nine patients (96.0%) were metastatic at diagnosis, and 9 patients were declared refractory during first-line treatment at a median of 8 months (range, 4 to 9 months), after receipt of the induction phase in 3 patients and the induction phase plus auto-HCT in 6 patients. Thirty-seven patients (72.5%) relapsed at a median of 19.0 months (interquartile range [IQR], 16.0 to 26.0 months) from diagnosis. Detailed patient and donor clinical information is reported in Table 1. The median age at study entry was 7.1 years (IQR, 5.3 to 9.1 years). The median follow-up after allo-HCT was 21.7 months (IQR, 7.6 to 38.1 months). Thirty-nine patients (76.5%) had undergone a prior auto-HCT. Allo-HCT was performed at a median of 20.4 months (IQR, 11.5

Table 1
Patient Characteristics (n = 51)

Characteristic	Value
Age at diagnosis, yr, median (IQR)	4.3 (3.0-6.3)
Sex, n (%)	
Male	32 (62.7)
Female	19 (37.3)
Number of previous auto-HCT, n (%)	
0	12 (23.5)
1	39 (76.5)
Disease status before HCT, n (%)	
Complete response	9 (17.6)
Very good partial response	10 (19.6)
Partial response	20 (39.2)
Stable disease	12 (23.6)
MYCN status, n (%)	
MYCN amplified	10 (19.6)
MYCN gain	9 (17.6)
MYCN nonamplified	21 (41.2)
NE	11 (21.6)
Indication for allo-HCT, n (%)	
HR disease without relapse or disease refractory to initial therapy	5 (9.8)
HR with disease relapse at least 6 mo after auto-HCT	35 (68.6)
HR refractory to initial therapy	9 (17.6)
Non-HR with disease relapse at least 6 mo after auto-HCT	2 (3.9)
Age at HCT, yr, median (IQR)	7.1 (5.3-9.1)
Time from diagnosis to HCT, yr, median (IQR)	2.2 (1.4-3.0)
Type of donor, n (%)	
MFD	27 (51.9)
MUD	24 (47.1)
Stem cell source, n (%)	
BM	45 (88.2)
PBSCs	6 (11.8)
Donor-recipient sex mismatch, n (%)	
Female/female	9 (17.6)
Female/male	12 (23.6)
Male/female	10 (19.6)
Male/male	18 (35.3)
Missing	2 (3.9)
Donor/recipient CMV serostatus, n (%)	
-/-	10 (19.6)
-/+	11 (21.6)
+/-	5 (9.8)
+/+	21 (41.2)
Missing	4 (7.8)
Follow-up after HCT, mo, median (IQR)	21.7 (7.6-38.1)

NE indicates not evaluable.
Amplification: in FISH analysis, >4-fold increase of the *MYCN* signal number in relation to the number of chromosome 2.
Gain: in FISH analysis, a 2- to 4- fold excess of *MYCN* copies in relation to the reference probe on chromosome 2.

to 28.4 months) after auto-HCT. Twenty patients (39.2%) were in partial response or stable disease at the time of allo-HCT. Twenty-seven patients underwent allo-HCT from an MFD (51.9%), and 24 underwent MUD allo-HCT (47.1%). The stem cell source was BM in 45 patients (88.2%) and PBSCs in 6 patients (11.8%). The median total nucleated cell count for those receiving BM grafts was 4.9×10^8/kg (IQR, 3.6 to 7.1 $\times$ 10^8/kg), and the median $CD34^+$ cell count for those receiving PBSC grafts was 11.3×10^6/kg (IQR, 6.2 to 19.9 $\times$ 10^6/kg). None of the patients received any consolidation or maintenance therapy after allo-HCT.

Primary Outcomes

Forty-six patients have died, 30 (65.2%) from disease progression; causes of death are reported in Table 2. No patient died from disease progression before day +100 after allo-HCT. The median follow-up of the 5 surviving eligible patients was 7.5 years (IQR, 6.3 to 9.0 years). The CuI of neutrophil and platelet engraftment at 100 days of the 51 patients was 97.9% ± 2.1% and 93.8% ± 3.5%, respectively. No patients experienced primary or secondary graft failure. Five-year, one-year and 100-days TRM was 29.4% ± 6.4%, 17.7% ± 5.3%, and 5.9% ± 3.3%, respectively (Figure 1A). Five-year TRM for patients receiving allo-HCT from MFD and MUD was 22.2% ± 8.0% and 37.5% ± 9.9% (p = .255), respectively (Figure 1B). Among patients receiving allo-HCT from MUD, five-year TRM for patients receiving a 9/10 or 10/10 match was 52.9% ± 15.8% and 30.0% ± 14.5% (p = .630), respectively. Five-year DFS was 11.8% ± 4.5% (Figure 1C). DFS for patients receiving allo-HCT from MFD and MUD was 14.8% ± 6.8% and 8.3% ± 5.6% (p = .086), respectively (Figure 1D). In patients receiving allo-HCT from MUD with 9/10 or 10/10 match, five-year DFS was not significantly different (7.1% ± 6.9% vs 10.0% ± 9.5% (p = .577). The univariable Cox proportional hazards regression testing clinical variables and their influence on 5-year TRM and DFS is reported in Table 3. For TRM, there was no association with the clinical variables analyzed, including sex, age at diagnosis, disease status before allo-HCT, previous HCT, time from diagnosis to allo-HCT, donor, cell source, donor's age, grades II to IV aGVHD or all stages of cGVHD. For DFS, receiving an allo-HCT within 12 months from the initial diagnosis, which occurred in 12 patients, and using BM as the graft source, were associated with superior DFS. Specifically, HCT earlier than 12 months from diagnosis compared to those greater than 12 months post-diagnosis had a DFS of 40.0% ± 21.9% vs 8.7% ± 4.2% (p = .013), while patients receiving BM compared to PBSC presented a DFS of 13.3% ± 13.1% vs 0% ± 0% (p < .001). We also analyzed the effect of aGVHD on DFS. Patients who developed grade II to IV aGVHD showed a tendency towards improved DFS, although this trend did not reach statistical significance. Moreover, when comparing the incidence of death due to disease progression between patients who developed grade II-IV aGVHD and those who did not, we did not find a statistically significant difference (p = .855).

Table 2
Causes of Death (n = 46)

Cause	No. (%)
Disease progression	30 (65.2)
Multiorgan failure	8 (17.4)
Septic shock	2 (4.3)
Hemorrhage	1 (2.2)
Chronic GVHD	1 (2.2)
Not available	4 (8.7)

Secondary Outcomes

The CuI of aGVHD at 100 days was 47.1 ± 7.0% grade II-IV and 15.7 ± 5.1% for grade III-IV. The CuI of grade II-IV aGVHD at 100 days was 41.2 ± 9.7% for patients receiving MFD allo-HCT and 53.5 ± 7.1% for recipients of MUD allo-HCT (*P* = .377). The CuI of grade III-IV aGVHD at 100 days was 15.4 ± 7.1% for patients receiving MFD allo-HCT and 17.4 ± 7.9% for MUD allo-HCT recipients (*P* = .920), respectively. The CuI of limited cGVHD was 19.8 ± 11.4%, and that of extensive cGVHD was 8.3 ± 3.3%. The CuI of limited cGVHD was 17.4 ± 6.1% for patients receiving MFD allo-HCT and 21.3 ± 8.9% for MUD allo-HCT recipients (*P* = .677), and the CuI of extensive cGVHD for the 2 groups was 6.7 ± 11.3% and 10.4 ± 10.0%, respectively (*P* = .830).

DISCUSSION

The choice of treatment for HR NB is complicated, considering the very low survival rates. Here we report the results of a prospective multicenter trial on the use of MFD or MUD allo-HCT using a RIC regimen for the treatment of HR NB. In this cohort, 90% overall mortality was recorded. In this scenario, TRM was low and related mainly to disease progression. Patients in the AIEOP registry undergoing allo-HCT for HR NB between 2002 and 2020 with a myeloablative conditioning regimen had a 5-year TRM of 48.4 ± 8.4%

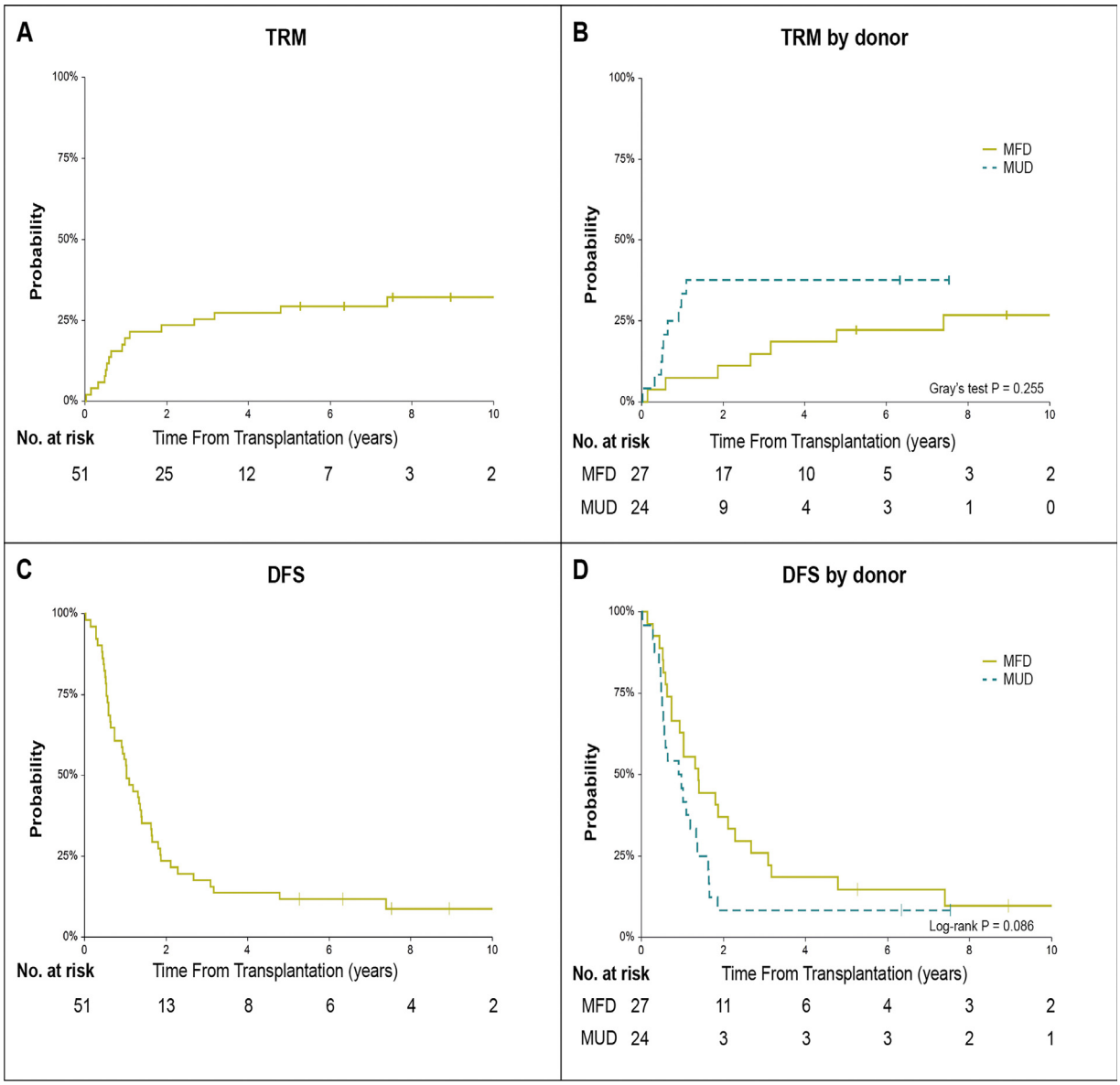

Figure 1. CuI of TRM for the entire cohort (A) and by donor type (B). Kaplan-Meier estimates of DFS for the entire cohort (C) and by donor type (D).

Table 3
Univariable Analysis of Clinical Variables and Their Influence on 5-Year TRM and DFS

Covariate	5-yr TRM		5-yr DFS	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Female sex	.8 (.5-1.4)	.433	1.1 (.8-1.5)	.580
Age at diagnosis <36 mo	1.1 (.6-2.1)	.697	.9 (.7-1.3)	.676
Complete remission before allo-HCT	1.0 (.7-1.4)	.895	1.2 (.9-1.5)	.258
MYCN amplification	1.2 (.6-2.4)	.640	.8 (.6-1.1)	.222
Previous auto-HCT	1.6 (.8-3.4)	.202	1.3 (.9-1.9)	.157
Time from diagnosis to allo-HCT <12 mo	1.8 (.6-5.0)	.265	2.0 (1.1-3.6)	**.002**
Donor (MFD)	1.5 (.9-2.6)	.093	1.3 (1.0-1.7)	.090
Cell source (BM)	1.6 (.7-3.5)	.231	2.3 (1.4-3.8)	<**.001**
Donor age <10 yr	1.4 (.7-3.0)	.355	1.2 (.8-1.8)	.309
aGVHD grade II-IV vs 0	.6 (.4-1.1)	.099	.7 (.5-1.0)	.052
Chronic GVHD	.7 (.3-1.5)	.346	.8 (.6-1.2)	.272

Bold type indicates statistical significance.
CI indicates confidence interval.

(Supplementary Table S1, Supplementary Figure S1). Although comparing our results with those from the AIEOP registry suggests that an RIC regimen may lower the incidence of TRM, it is important to interpret this data cautiously because of the high heterogeneity of the 2 cohorts. However, given these findings, a phase III study comparing myeloablative and RIC regimens may be proposed. Indeed, despite low transplantation-related toxicity, the 5-year DFS probabilities from transplantation were dismal. We also noted a high CuI of aGVHD in our cohort despite the use of standard prophylactic regimens, as reported by other authors [15], suggesting that the inclusion of alternative prophylactics may be considered in this context. These results are comparable to findings in previous retrospective studies on NB patients receiving allo-HCT. Hale et al. [16] analyzed 143 allo-HCTs in patients with NB in the CIBMTR registry and reported a 5-year TRM and DFS of 25% and 20%, respectively. Hara et al. [15] reported the outcomes of 22 patients receiving allo-HCT from MSD and MFD, with a 3-year progression-free survival and OS of 15.3% and 16.9%, respectively. Regarding the clinical outcomes impacting TRM, no significant associations were identified in our cohort. Interestingly, however, patients undergoing allo-HCT within 12 months after diagnosis with BM as the stem cell source had a higher DFS probability. Moreover, patients who developed grade II-IV aGVHD exhibited a trend toward a better DFS that was not associated with a lower rate of death from disease progression. A graft-versus-neuroblastoma effect was described for *in vitro* models [19,20]; however, no definitive clinical evidence has been provided [21]. Our data thus support the concept that GVHD occurrence does not predict a lower disease progression in NB patients, as was also suggested by the CIBMTR experience [16]. The use of post-transplantation therapeutic strategies to improve the allogeneic effect has been hypothesized. In fact, evidence of an effect of donor lymphocyte infusion was demonstrated in animal models and in a case report; however, no definitive evidence from clinical trials is available [19,22]. Additionally, the use of adoptive donor natural killer (NK) cell therapy has been explored in recent years based on the evidence reported for acute leukemia [23,24]. Illhardt et al. [25] reported the results of 26 patients affected by relapsed/refractory (R/R) NB undergoing haploidentical HCT showing an OS of 19% and an EFS of 23%. Of note, outcomes were similar to those previously reported for MUD and sibling donors without a significant effect of KIR mismatch. A later study from Flaadt et al. [26] reported the results of haploidentical HCT followed by anti-GD2 antibody and IL-2 in R/R NB that resulted in a 5-year EFS of 43%, suggesting that the NK-mediated graft-versus-neuroblastoma effect may be enhanced by post-HCT immunotherapy. Future studies could provide more insight into the graft-versus-neuroblastoma effect in the haploidentical setting. These results also should be interpreted in an expanding scenario of novel approaches that may be integrated in the post-transplantation setting, such as GD2-targeting chimeric antigen receptor T cell therapy, both autologous and allogeneic, which has shown highly promising results for R/R NB [11], and other targeted therapies, such as lorlatinib in ALK-driven R/R NB, or other immunotherapies [27,28].

CONCLUSION

In summary, this study confirms that HLA-matched allo-HCT based on an RIC regimen in HR NB is feasible and associated with low TRM. Despite this safety profile, however, patient prognosis remains dismal owing to a high frequency of disease progression. The benefit of allo-HCT with an RIC regimen appears to be more effective in disease control when performed within 12 moths after diagnosis and using BM as the stem cell source. In the setting of HR NB, donor T cell-mediated alloreactivity did not result into a significant graft-versus-neuroblastoma effect capable of controlling disease recurrence or progression.

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Data availability statement: The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.03.002.

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