Clinical case

Breakthrough CAR-T Therapy in Refractory B-Cell Lymphoma: MIOT International Chennai, India Case Study

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Abstract: CAR-T cell therapy has emerged as a promising treatment for relapsed/refractory B-cell non-Hodgkin lymphoma (R/R B-NHL), especially in patients with limited therapeutic options. We report the case of a 60-year-old male with primary chemotherapy-refractory diffuse large B-cell lymphoma (DLBCL) and comorbidities including diabetes, hypertension, and stable coronary artery disease, treated with anti-CD19 CAR-T cell therapy (NEXCAR19) at MIOT International, Chennai. Following disease progression after seven cycles of R-CHOP chemotherapy and consolidation radiotherapy, lymphocyte apheresis was performed, yielding sufficient starting material for CAR-T cell production. The patient received fludarabine–cyclophosphamide conditioning followed by infusion of 100 mL of NEXCAR19 CAR-T cells, which was well tolerated without cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. PET-CT at day +29 demonstrated a marked metabolic response (Deauville score 4). Low-dose nivolumab maintenance therapy and IMRT-based consolidation radiotherapy to residual abdominal nodes were introduced to enhance remission durability and CAR-T sensitization. This case illustrates the feasibility, safety, and promising early efficacy of anti-CD19 CAR-T therapy in chemo-refractory DLBCL and highlights the potential benefit of integrating immunotherapy with targeted radiotherapy. Long-term follow-up will determine relapse risk and sustained response.

Keyword: CAR-T therapy, diffuse large B-cell lymphoma, NEXCAR19, refractory lymphoma, immunotherapy, case report.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the most effective curative approach for numerous hematological malignancies. However, the major limitation in transplant accessibility remains the scarcity of suitable matched sibling donors, coupled with the high costs and logistical challenges associated with matched unrelated donor (MUD) or umbilical cord blood sources. Haploidentical transplantation (haplo-HSCT), utilizing donors who share only half of the human leukocyte antigen (HLA) haplotype, has emerged as a pragmatic and highly effective alternative. Its primary advantages—immediate donor availability within the patient's family, reduced costs, and simplified logistics—have significantly improved transplant accessibility, particularly in resource-constrained settings such as India. Historically, haploidentical transplantation faced challenges including severe graft-versus-host disease (GVHD), graft rejection, delayed immune recovery, and elevated transplant-related mortality (TRM). However, recent advances have largely overcome these obstacles, transforming haplo-HSCT into a reliable and increasingly standardized therapeutic option.

Case Presentation

A nine-year-old boy from Madurai, a smaller city in the southern Indian state of Tamil Nadu, presented with high fever and marked pallor. He was the only child of his parents, and the family had limited financial means. Initial evaluation at a local hospital revealed abnormal blood counts suspicious for acute leukemia. The child was promptly referred to a state-run tertiary care center,

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where bone marrow examination confirmed the diagnosis of acute myeloid leukemia (AML). Cytogenetic analysis showed a normal karyotype, and molecular tests were negative for NPM1 and FLT3 mutations.

The patient was started on standard induction chemotherapy with daunorubicin and cytarabine. After the first induction cycle, he had persistent disease (induction failure), which necessitated a second induction cycle with the same regimen. The second induction achieved a complete remission.

He then received three cycles of high-dose cytarabine-based consolidation therapy as per standard pediatric AML protocols. The cost of this intensive treatment forced his father to liquidate nearly all of the family's remaining property to finance the therapy, effectively exhausting their financial resources. Without a matched sibling donor and given the family's strained finances, a potentially curative allogeneic stem cell transplant was not pursued at that time. The boy was discharged from the tertiary center in remission after completing consolidation.

Unfortunately, about eight months after completing therapy, he suffered a relapse of AML. His family sought further treatment at multiple hospitals; physicians universally agreed that re-induction chemotherapy followed by an allogeneic hematopoietic stem cell transplant (HSCT) offered the only chance of cure. With no related donor available, a search for a matched unrelated donor (MUD) was initiated. However, no suitable donor was found in the national registries, and the cost of obtaining a donor graft from international registries was prohibitive for his family. Without the possibility of a transplant, curative treatment was essentially out of reach, leading some centers to recommend only palliative care to manage his symptoms.

In their determination to fight the disease, the family pursued several salvage chemotherapy regimens for the boy at different hospitals in an effort to hold the leukemia at bay. These treatments, however, were non-curative in nature and provided only temporary disease control. By this time, his parents were distraught and nearly out of options. It was at this juncture that a national non-profit organization dedicated to funding cancer care for children became involved in his case. Through the charity's support, the patient was referred to our tertiary care center, which collaborates with the organization to provide treatment for children with cancer from underprivileged backgrounds.

When he arrived at our institution, the child was in frank relapse despite multiple prior therapies, and there was still no suitable HLA-matched donor available. After careful evaluation, our team decided to attempt one more remission induction in hopes of creating an opportunity for a definitive transplant. He was treated with a salvage regimen of fludarabine, cytarabine, and idarubicin (FLA-Ida). Remarkably, this achieved a second complete remission, with minimal residual disease by flow cytometry falling below 0.01%.

Despite this hard-won remission, we knew that without proceeding to HSCT, the leukemia would almost certainly recur again. Unfortunately, a conventional MUD transplant was still not feasible—there was no available donor match, and the cost remained well beyond the family's means. Given the lack of any conventional donor options and the family's financial constraints, we explored alternative donor strategies. We proposed a haploidentical HSCT using a half-matched parent as the donor. His father was identified as a suitable donor, providing an immediately available graft source at a fraction of the cost of an unrelated donor. Knowing this was their only child, his parents were willing to attempt anything that offered a chance of cure, and the haploidentical approach was both medically viable and financially within reach. After comprehensive counseling about the risks and benefits, the family consented to proceed with the haploidentical transplant as the final hope for their son.

The patient subsequently underwent a T-cell–replete haploidentical transplant with his father as the donor. The conditioning regimen and graft-versus-host disease prophylaxis were tailored to the haploidentical setting (including post-transplant cyclophosphamide). The transplant course was uneventful: he achieved prompt engraftment with full donor chimerism and no severe acute complications. After appropriate supportive care, he was discharged from the transplant unit in stable condition.

As of the latest follow-up, nearly eight years post-transplant, the child remains in complete remission. He is off all immunosuppressive therapy and shows no evidence of disease recurrence. Apart from a mild skin hyperpigmentation (possibly a minor manifestation of chronic GVHD), he has

had no significant late complications. His growth and developmental parameters are age-appropriate, and he has resumed normal childhood activities.

This case underscores the formidable socioeconomic barriers to advanced leukemia treatment in resource-limited settings. It also highlights the potential of haploidentical transplantation as a curative option when standard donor sources are unavailable or unaffordable. Finally, it demonstrates that with an available haploidentical family donor and charitable support, even a potentially fatal pediatric AML relapse can be successfully treated.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapy for many hematologic malignancies. However, its success hinges on donor availability, and only about 30% of patients have an HLA-matched sibling donor. Patients lacking a match often cannot find or afford a matched unrelated donor or cord blood graft, especially in countries like India where donor registries are limited. In such cases, haploidentical (half-matched) family donors have emerged as a critical alternative. Virtually every patient has at least one haploidentical relative available, and these donors can be accessed immediately without international registries, greatly reducing costs and delays Reflecting these advantages, haploidentical transplantation is now an increasingly popular option worldwide, helping bridge the gap in access to transplant therapy for patients who previously had no donor.

Historically, early attempts at haploidentical HSCT were plagued by high rates of graft rejection and severe graft-versus-host disease (GVHD) due to major HLA mismatch. Over the past decade, research advances have overcome many of these barriers, leading to markedly improved outcomes. Various immunomodulatory strategies now enable safe crossing of HLA barriers

For example, ex vivo T-cell depletion of the graft (often with "megadose" CD34 stem cells) and selective removal of alloreactive lymphocytes were developed to prevent GVHD

Equally transformative is the use of post-transplant cyclophosphamide (PTCy) for in vivo T-cell inactivation, which largely eliminates the previously formidable GVHD risk.

Concurrently, conditioning regimens have been refined to broaden the applicability of haploidentical HSCT. Reduced-intensity conditioning (RIC) protocols now allow older or medically unfit patients to undergo transplantation with acceptable toxicity. Additionally, donor selection algorithms have evolved to optimize outcomes—evidence suggests that younger donors and certain donor–recipient relationships (e.g. a parent donor or favorable killer immunoglobulin-like receptor mismatches) can reduce GVHD and relapse risk. As a result of these advances, haploidentical transplantation has progressed from an experimental last resort to a routinely standardized practice at many centers. The use of haploidentical donors has surged by over 500% in the last decade, reflecting its success in expanding the donor pool and reducing disparities in access to curative transplantation. Here we review recent innovations in conditioning, GVHD prophylaxis, and donor strategies that have solidified haploidentical HSCT as a mainstream solution to donor unavailability in both high- and low-resource settings.

Haploidentical transplant –How to cross the HLA barrier and tune the immune cells:

The major obstacle for the success of a Haploidentical transplant is the host and donor T cell responses to alloreactive HLA molecules resulting in a high incidence of graft rejection and unacceptable GVHD. The basic design of a haploidentical transplant protocol should adequately address this issue. Three major approaches were tried7.

1. To do an in vitro T cell depletion and give "mega doses" of CD34+ cells (>10 x 106 cells /kg) -Perugia approach.

2. Selective depletion of CD3/CD19 positive cells in the graft – German approach.

3. In vivo alloreactive T cell depletion using post-transplant cyclophosphamide – Baltimore approach.

Still research is on to prove the superiority of one approach over the other with each having its own pros and cons. The Perugia approach definitely reduced the incidence of graft rejection but a major disadvantage was delayed immune recovery due to paucity of T cells in the graft. The use of

ATG further increased the chances of life threatening infections negating the overall outcome by increased non-relapse mortality. More challenging techniques like adoptive transfer of gene modified T cells, Tregs and pathogen specific T cells are of some benefit but need expertise and wide implementation is a concern. The Germans came up with a new technique of depleting CD3/CD19

cells in the graft and reduced intensity conditioning regimens in transplanting older individuals with EFS of 25% at 2 years.

Let's compare the available alternate donor sources:

Table 1. Advantages and disadvantages of alternative stem cell donor sources

Source	Advantages	Disadvantages
Unrelated donor	Mature data available High CD34+ cell dose Accepted modality of therapy	Time and cost to procure cells especially in countries like India where registry is still small
Haploidentical donor	Easy donor availability High cell dose and scope for graft manipulation	Risk of graft failure and poor immune recovery
Umbilical cord	Easy availability Acceptable mismatches Usage of multiple units	Low cells Failure of engraftment No scope for DLI

Table 2. Comparative characteristics of different donor sources in allogeneic hematopoietic stem cell transplantation

Donor	Availability	Reaccess	Cost	Rejection risk	Sped of Engraftment	GVHD Risk	GraftVs Leukemia	Immune Reconstitution
Matched Sibling	20%	Fast	Low	Low	Fast	Low	T cells	Fast
Unrelated Bone Marrow	10/10 – 40% 9/10 – 70%	Slow	High	Low	Moderate	Moderate	T cells	Moderate
Unrelated Cord blood	>4/6 – 70%	No	High	Low	Slow	Low	T cells	Slow
Haploidentical transplant	>90%	Immediate	Low	Low	Fast	Low	NK cells	Very Slow

Now the problem shifts from none to many:

In the light of above data and unavailability of another donor source, we decided to proceed with haploidentical transplant in this case. Now high resolution HLA typing revealed both the parents are a perfect Haplomatch to him. Now it was our turn to choose the best donor for him. In few other cases, we had faced a similar situation with even up to four haploidentical donors available.

In unrelated donor search, we mainly focus on the degree of HLA mismatch to decide on the best donor but the situation is entirely different in this setting. Careful selection of donors will have an impact on graft rejection, GVHD and Transplantation Related Mortality. The killer immunoglobulin-like receptor (KIR) system plays an important role in defining alloreactivity of donor natural killer (NK) cells against recipients' blasts. In a recent review by Wang et al2 from China, they proposed few practical points for the choosing the donors.

- The degree of HLA mismatch or match had no impact on the Transplant related mortality (TRM), GVHD or relapse risk.
- Donors less than 30 years had low incidence of GVHD.
- With respect to Transplant related Mortality young male donors had a better outcome compared to older and female donors.
- Mother donors were associated with higher GVHD risk irrespective of recipient sex.
- Mother to son was associated with high TRM and lower survival.
- Father to son is preferred.
- If siblings less than 30 years are available they are preferred over parent donors.
- Older sisters (>30 years) pose a high TRM risk to male recipients.
- Offspring donors are preferred over sibling donors.

- Exposure of the developing foetus to maternal cells, which occurs during pregnancy, can lead to either immunity or tolerance of non-inherited maternal HLA Antigens (NIMA) and subsequently have an effect on transplant outcome. Non-Inherited Paternal and Maternal antigen (NIMA/NIPA) mismatch doesn't have an impact on the TRM, chronic GVHD, relapse or survival.

But controversy still persisted as the Perugia group favoured a mother donor for better relapse free survival.

KIR Mismatch in Haploidentical Setting.

The Perugia group established the importance of natural killer (NK) cell alloreactivity mediated by killer immunoglobulin-like receptor (KIR) mismatches in promoting graft-versus-leukemia (GVL) effects in haploidentical transplantation. NK cells express inhibitory KIR receptors recognizing specific HLA class I alleles; absence of these ligands in the recipient (KIR mismatch) enables NK cells to target leukemic cells effectively, thus reducing relapse risk and GVHD incidence. Two main KIR haplotypes (A and B) have been described, with haplotype B exhibiting more activating receptors. In T-cell replete haploidentical protocols using post-transplant cyclophosphamide (PTCy), KIR mismatch significantly enhances transplant outcomes. In our presented case, KIR typing revealed a mismatch favoring the mother as the optimal donor.

T-Replete Haploidentical Transplant: Strategies to Minimize GVHD

The primary challenge in T-replete haploidentical transplantation is significant graft-versus-host disease (GVHD). Several approaches have been explored to effectively mitigate this risk:

1. GIAC Protocol: This Chinese regimen utilizes G-CSF-mobilized peripheral blood stem cells (PBSCs), coupled with intensive immunosuppression including cyclosporine, mycophenolate mofetil (MMF), and anti-thymocyte globulin (ATG). This strategy achieved nearly 100% engraftment, with approximately 60% three-year survival rates in both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), but severe GVHD (grade III-IV) remained around 15%.
2. Rapamycin-Based Prophylaxis: The Milan group explored rapamycin, an immunosuppressive agent selectively preserving regulatory T-cells (Tregs), in combination with MMF. Their study demonstrated acceptable GVHD incidence, with non-relapse mortality (NRM) around 17% at one year; however, longer follow-up is required for comprehensive evaluation.
3. Post-Transplant Cyclophosphamide (PTCy): The Johns Hopkins group pioneered administering cyclophosphamide early after transplantation (days +3 and +4), effectively depleting donor and recipient alloreactive T-cells while sparing hematopoietic stem cells. Using a non-myeloablative regimen combining fludarabine, low-dose total body irradiation (TBI), and cyclophosphamide, they achieved over 87% successful engraftment and notably low severe GVHD rates (<7%). Although initial studies showed a relatively high relapse rate, adjustments in conditioning regimens (incorporating agents like melphalan and busulfan) have substantially improved outcomes, now making PTCy-based regimens the global standard.

These approaches highlight ongoing innovations to enhance safety and efficacy in T-replete haploidentical HSCT, enabling broad clinical adoption and improved patient outcomes.

Our Experience and Practical Insights

Transplant protocols vary across regions—Europe often favors CD34+ selection, while China employs intensive immunosuppression. At our center, post-transplant cyclophosphamide (PTCy) has proven to be a practical and reproducible approach in the Indian context.

In a representative case, a patient received fludarabine, melphalan, and thiotepa-based conditioning, followed by PTCy on days +3 and +4. Engraftment was successful, with neutrophils on day +17 and platelets on day +19. GVHD prophylaxis with cyclosporine and MMF was well tolerated, and donor chimerism at day +30 reached 90%. The post-transplant course was uneventful except for transient febrile neutropenia.

Advantages of PTCy-based GVHD prophylaxis include:

- Ease of administration
- Broad applicability
- Lower non-relapse and infection-related mortality

Practical post-transplant tips:

- Fever in the first five days is common due to cytokine release—treat empirically, avoiding early immunosuppressants like steroids to preserve PTCy efficacy
- Infection vigilance remains crucial, similar to MUD settings

The same patient remains in remission nearly eight years post-transplant, with normal development and minimal late effects.

Donor Lymphocyte Infusion (DLI) in Relapse

DLI can help manage post-transplant relapse but carries GVHD risk. Early studies showed up to 50% mortality due to GVHD. In more recent data, DLI in haploidentical transplants led to a 2-year survival of 21% versus 9% in non-DLI patients, with remission achieved in one-third when combined with chemotherapy. However, relapse with loss of donor chimerism predicts poorer outcomes, and such patients may benefit from preemptive or prophylactic cellular therapies.

Real-World Comparisons

T-replete vs T-deplete:

In a comparison by Ciurea et al., T-replete transplants showed better overall survival (OS), progression-free survival (PFS), immune reconstitution, and lower GVHD and infection rates than T-depleted transplants.

T-replete vs Cord Blood:

Although both have similar relapse risks, T-replete haploidentical transplants result in faster engraftment and lower grade IV GVHD. Considering cost, availability, and simplicity, T-replete haplo-HSCT is likely to be preferred over double cord blood transplants in the future.

Institutional Experience and Practical Management Insights

At MIOT International, Chennai, our institutional bone marrow transplant (BMT) program has accumulated significant experience, successfully performing over 200 haploidentical hematopoietic stem cell transplants (HSCT) from 2012 to 2024 as part of a broader transplantation effort involving more than 600 allogeneic transplants. This extensive clinical experience positions our center among leading Indian institutions providing robust outcomes with haploidentical transplantation.

Our preferred protocol utilizes a T-cell replete approach with post-transplant cyclophosphamide (PTCy) for in vivo depletion of alloreactive T-cells, combined with a conditioning regimen consisting of fludarabine, melphalan, and thiotepa. This regimen reliably achieves prompt engraftment, minimal incidence of severe acute graft-versus-host disease (GVHD), manageable chronic GVHD rates, and favorable patient outcomes (Kumar et al., 2017; Subash et al., 2018).

Building on the standard PTCy platform, our institution evaluated the impact of reducing the standard dose of cyclophosphamide from 50 mg/kg to 25 mg/kg (low-dose PTCy). This strategy, known as the "Chennai Protocol," demonstrated efficacy in reducing GVHD risk without compromising graft engraftment or survival outcomes (Kumar et al., 2021). Our clinical results with low-dose PTCy confirmed adequate immune tolerance induction, lower transplant-related toxicities, reduced complications, and promising patient survival.

Another novel strategy successfully explored at our center was the judicious use of plerixafor for healthy haploidentical donors failing initial stem cell mobilization. We reported excellent safety profiles and significantly enhanced yields of peripheral blood stem cells (PBSC), enabling successful transplantation without donor-related complications (Subash et al., 2018). This strategy substantially improved transplant logistics, particularly in haploidentical settings, ensuring timely transplant availability even in initially difficult mobilizers.

Moreover, recognizing the persistent clinical challenge of GVHD despite standard prophylaxis, we explored innovative approaches including incorporation of targeted JAK inhibition through the drug Ruxolitinib. Our group published pioneering data indicating that Ruxolitinib prophylaxis effectively mitigated GVHD incidence and severity, enabling better immune modulation post-haploidentical HSCT and enhancing patient quality of life and outcomes (Kumar et al., 2022).

Through the adoption of these pioneering protocols—low-dose cyclophosphamide conditioning ("Chennai Protocol"), rescue stem cell mobilization with plerixafor, and JAK inhibitor-based GVHD prophylaxis—we have demonstrated consistently superior patient outcomes, affordability, ease of implementation, and reproducibility within resource-limited Indian healthcare environments.

Thus, the success of haploidentical transplantation at MIOT International has been driven by innovation, rigorous clinical evaluation, and adaptation of globally validated concepts into locally

feasible and effective transplant protocols, significantly expanding transplant accessibility to patients otherwise disadvantaged by donor availability and economic barriers.

Discussion:

Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has evolved from an experimental approach to a globally accepted therapeutic modality for patients lacking HLA-matched donors. The findings from MIOT International Hospital, Chennai, India, add to the growing body of evidence demonstrating that optimized T-cell replete transplantation with post-transplant cyclophosphamide (PTCy) can achieve clinical outcomes comparable to those of matched sibling or unrelated donor transplants. The results from over 200 haploidentical transplants performed at the institution confirm that with proper conditioning and GVHD prophylaxis, reliable engraftment, low toxicity, and durable survival can be achieved even in resource-limited environments.

Compared with earlier studies that relied heavily on T-cell depletion (the Perugia or German approaches), the current PTCy-based strategy provides a more practical and reproducible platform, especially in centers with limited laboratory infrastructure. The "Chennai Protocol," utilizing low-dose PTCy (25 mg/kg), offers an important advancement by reducing treatment-related morbidity while maintaining immune tolerance and engraftment stability. This aligns with global observations by Bashey et al. (2014) and Ciurea et al. (2013), who emphasized that in vivo T-cell modulation using PTCy achieves a favorable balance between GVHD prevention and graft-versus-leukemia (GVL) effects.

The institutional innovation of using plerixafor for poor mobilizers further enhances donor feasibility, addressing one of the main logistical limitations in haploidentical settings. Moreover, prophylactic integration of ruxolitinib, as demonstrated in the MIOT experience, reflects a growing trend toward targeted immune modulation in transplantation, complementing emerging international data on JAK inhibition as a tool to minimize GVHD without impairing immune reconstitution.

The presented pediatric AML case underscores both the curative potential and socioeconomic impact of haploidentical transplantation. It exemplifies how the accessibility of a family donor and charitable medical support can transform outcomes in patients otherwise excluded from curative therapy due to financial constraints. The eight-year disease-free survival reported in this case compares favorably with previously published long-term outcomes in similar cohorts, confirming the durability of the haploidentical approach.

In a broader context, these findings support the view that haplo-HSCT bridges a critical gap in global transplant accessibility. As donor registries remain limited in many developing regions, the ability to use family members as immediate donors can substantially expand the availability of curative transplantation. Continued refinement of conditioning regimens, GVHD prophylaxis, and donor selection—particularly leveraging KIR mismatches and NK-cell–mediated GVL effects—will be central to improving relapse control and immune recovery.

Future research should focus on multicenter prospective studies validating low-dose PTCy protocols, integration of immune monitoring tools to optimize donor–recipient matching, and development of combined strategies that incorporate NK-cell therapy, donor lymphocyte infusions, and CAR-T technologies. Such innovations will not only strengthen the curative potential of haploidentical transplantation but also further democratize access to advanced hematologic care worldwide.

Conclusions

1. Universal Donor Availability:

Nearly all patients have immediate access to at least one haploidentical donor within their family, eliminating the delays and expenses associated with matched unrelated donor (MUD) or cord blood searches.

2. Cost-Effectiveness: Haploidentical transplantation represents an economically feasible and practical curative approach for leukemia patients lacking matched sibling donors, especially important in resource-constrained settings.

3. Practical Advantages:

Compared to MUD or umbilical cord blood transplantation, haploidentical transplantation offers rapid donor availability, significantly reduced costs, simplified logistics, and ease of repeated donor cell access.

4. Evolution from T-cell Depletion:

Traditional ex vivo T-cell depletion approaches (e.g., Perugia protocol) use "mega-doses" of CD34+ cells. Despite achieving high engraftment rates, these methods lead to delayed immune recovery and increased susceptibility to life-threatening infections.

5. Promising Emerging Techniques:

Novel methods like adoptive immunotherapy (e.g., virus-specific T-cells, gene-modified donor T-cells), selective depletion of alloreactive T-cells, and regulatory T-cell infusion hold significant promise but require specialized expertise and infrastructure.

6. T-cell Replete Protocol with PTCy:

The T-cell replete haploidentical transplant protocol using reduced-intensity conditioning (RIC) and post-transplant cyclophosphamide (PTCy, Hopkins approach) is now globally accepted and widely implemented, including at our center, due to its reproducibility, affordability, and favorable outcomes.

7. Institutional Innovations (Chennai Protocol):

Our institutional experience highlights success with lower-dose (25 mg/kg) PTCy ("Chennai Protocol"), demonstrating effective GVHD prophylaxis, lower toxicity, rapid engraftment, reduced transplant-related mortality, and overall cost reduction.

8. Management of Poor Donor Mobilizers:

Administration of plerixafor to healthy haploidentical donors failing initial mobilization has proven effective, safe, and logistically beneficial, improving transplant outcomes by ensuring timely and adequate stem cell harvest.

9. Novel GVHD Prophylaxis (Ruxolitinib):

Our institutional experience indicates that incorporating ruxolitinib into GVHD prophylaxis regimens significantly reduces GVHD incidence and severity, thus enhancing immune recovery, reducing complications, and improving patient quality of life post-transplant.

10. Relapse Mitigation Strategies:

T-cell replete haploidentical transplantation leveraging killer immunoglobulin receptor (KIR) mismatches, optimized donor selection (including maternal donors), innovative conditioning regimens, NK-cell therapies, and maintenance approaches are actively being investigated and hold promise in further reducing relapse risks.

Authors' contribution

Conceptualization, K.K., Dr.S; methodology, K.K.; validation, K.K.; investigation, K.K.; resources, K.K., data curation, K.K.; writing—original draft preparation, K.K.; writing—review and editing, K.K., Dr.S.; visualization, K.K.; supervision, K.K., Dr.S.; project administration, K.K., Dr.S. All authors have read and agreed to the published version of the manuscript.

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Ethics approval

Ethical review and approval were waived for this study as it is a retrospective description of a single treated patient, presented with informed consent and without any intervention beyond standard clinical care.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. **Data Availability Statement**

No new data were created in this study. Data supporting the findings are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare no conflict of interest. The funders had no role in the design, data collection, analysis, or decision to publish.

Abbreviations

AML	Acute Myeloid Leukemia
ATG	Anti-Thymocyte Globulin
CAR-T	Chimeric Antigen Receptor T-cell
DLI	Donor Lymphocyte Infusion
EFS	Event-Free Survival
FLA-Ida	Fludarabine, Cytarabine, and Idarubicin regimen
GVHD	Graft-Versus-Host Disease
GVL	Graft-Versus-Leukemia
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic Stem Cell Transplantation
KIR	Killer Immunoglobulin-like Receptor
MMF	Mycophenolate Mofetil
MUD	Matched Unrelated Donor
NK	Natural Killer (cell)
NIMA	Non-Inherited Maternal Antigens
NIPA	Non-Inherited Paternal Antigens
NRM	Non-Relapse Mortality
PBSC	Peripheral Blood Stem Cells
PTCy	Post-Transplant Cyclophosphamide
RIC	Reduced-Intensity Conditioning
TBI	Total Body Irradiation
TRM	Transplant-Related Mortality

References

[1] Selleslag D. Haploidentical stem cell transplantation in adults: novel strategies and future directions. Belg J Hematol. 2012;3:74-81.

[2] Kumar K, Subash C. A study to identify correlation of hematopoietic progenitor cell (XN-HPC) by Sysmex cell counters with final yield of CD34+ stem cells. Blood. 2017;130(Suppl 1):5458.

[3] Subash C, Kumar K. On demand plerixafor as a rescue strategy in healthy donors to augment peripheral blood stem cell collection in haploidentical transplants. Blood. 2018;132(Suppl 1):5642.

[4] Kumar K, Subash C. Experience of low dose (25 mg/kg) cyclophosphamide (Chennai protocol) as post-transplantation cyclophosphamide (PTCy) in haploidentical transplants. Blood. 2021;138(Suppl 1):4857.

[5] Kumar K, Subash C. Ruxolitinib as GVHD prophylaxis in haploidentical transplantation: clinical outcomes and immune modulation insights from South India. Blood. 2022;140(Suppl 1):6398.

[6] Handgretinger R. Haploidentical transplantation: the search for the best donor. Blood. 2014;124(6):827-828.

[7] Ghiso A, Raiola AM, Gualandi F, Dominietto A, et al. Donor lymphocyte infusion after haploidentical BMT with post-transplant cyclophosphamide. Bone Marrow Transplant. 2014;50(1):56-61. https://doi.org/10.1038/bmt.2014.217.

[8] Ciurea SO, Champlin RE. Donor selection in T-cell replete haploidentical hematopoietic stem cell transplantation: knowns, unknowns, and controversies. Biol Blood Marrow Transplant. 2013;19(2):180-184.

[9] Schwarer AP, Bollard G, Kapuscinski M, Muirhead J, et al. Long-term follow-up of a pilot study using a chemotherapy-alone protocol for killer Ig-like receptor-ligand-mismatched haploidentical hematopoietic SCT. Bone Marrow Transplant. 2011;46(10):1331-1338.

[10] Chang YJ, Huang XJ. Haploidentical SCT: the mechanisms underlying the crossing of HLA barriers. Bone Marrow Transplant. 2014;49(7):873-879.

[11] Bayraktar UD, Ciurea SO. Strategies in haploidentical stem cell transplantation in adults. Turk J Haematol. 2013;30(4):342-350.

[12] Solh M. Haploidentical vs cord blood transplantation for adults with acute myelogenous leukemia. World J Stem Cells. 2014;6(4):371-379.

[13] Bashey A, Solomon SR. T-cell replete haploidentical donor transplantation using post-transplant cyclophosphamide: an emerging standard-of-care option for patients who lack an HLA-identical sibling donor. Bone Marrow Transplant. 2014;49(8):999-1008.

[14] Ciurea SO, Mulanovich V, Saliba RM, Bayraktar UD, Jiang Y, Bassett R, et al. Improved early outcomes using a T-cell replete graft compared with T-cell depleted haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2012;18(12):1835-1844.