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Reduced Intensity Conditioning with Thiotepa-Fludarabine-Busulphan (TBF) and Post-Transplant Cyclophosphamide (PTC) Results in Rapid Complete Donor T-cell Chimerism in Haploidentical Recipients with Acute Myeloid Leukaemia

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INTRODUCTION

Allogeneic stem cell transplant (SCT) offers the best prospect of long-term survival for the majority of patients with intermediate and high-risk acute myeloid leukaemia (AML). However, huge diversity in the human leukocyte antigen (HLA) gene complex means identifying a suitably matched donor can be challenging [1]. While up to 30% of patients may have a fully matched sibling, the probability of identifying a matched unrelated donor (MUD) for the remaining patients ranges from 80% in Caucasian patients to less than 20% in ethnic minority groups[2]. Alternative donor sources are therefore an appealing option, and estimates suggest that 95% of patients have at least one haploidentical match[3]. The optimal conditioning regimen for haploidentical transplant remains unclear, but the emerging tolerability and success of post-transplant cyclophosphamide-based regimens has placed them at the forefront of development. Robust T-cell engraftment is critical to the graft versus leukaemia effect, which is pivotal to the success of SCT in AML.

AIM

The inherent bidirectional alloreactivity of a haploidentical transplant risks poor engraftment, therefore, we assessed whole blood and T-cell engraftment in haploidentical recipients with reduced-intensity TBF- PTC conditioning.

METHOD

We retrospectively analysed chimerism results of all recipients of reduced-intensity conditioned haploidentical stem cell transplants for AML at our institution and compared these to contemporaneous sibling and matched unrelated donor transplant. Institution policy dictates that transplant recipients undergo whole blood and CD3 T-cell selected donor recipient chimerism assessment routinely at day +30, +60, +90 and +120, and thereafter as clinically indicated. The Promega PowerPlex® 16HS system was used for DNA typing by Small Tandem Repeat (STR) analysis, and complete chimerism was defined by >95% donor cells. The probabilities of achieving complete whole blood, and T-cell donor chimerism, and of relapse were estimated using the Kaplan Meyer method and compared by log-rank test.

RESULTS

73 patients underwent reduced intensity SCT for AML between 2005 and 2018 and had sufficient chimerism follow-up. The number of patients undergoing haploidentical, sibling and matched unrelated donor transplants were 10, 24 and 39 respectively. At 93%, the overall achievement of complete whole blood donor chimerism was high in the cohort, but was significantly higher and attained more rapidly in the haploidentical group (probability of complete chimerism 100%, 73.9% and 92.3% at day +120 in the haploidentical, sibling and MUD recipients respectively (p=0.001), occurring at a median of 36, 52 and 40 days (p<0.001). The median time to complete T-cell chimerism was 36, 77 and 93 days. Failure to achieve complete T-cell chimerism by day +120 was associated with a significantly higher rate of relapse (3-year probability of relapse 39.5% vs 16.9%, p=0.015).

Figure 1

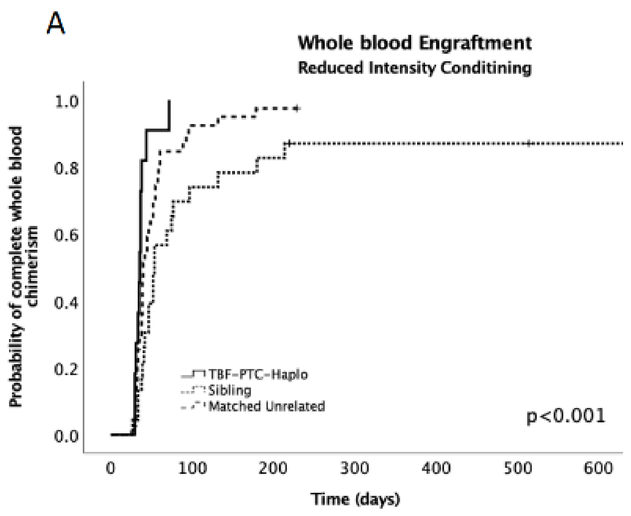

Figure 1A: Kaplan- Meier Curve showing probability of achieving whole blood chimerism depending on donor regimen

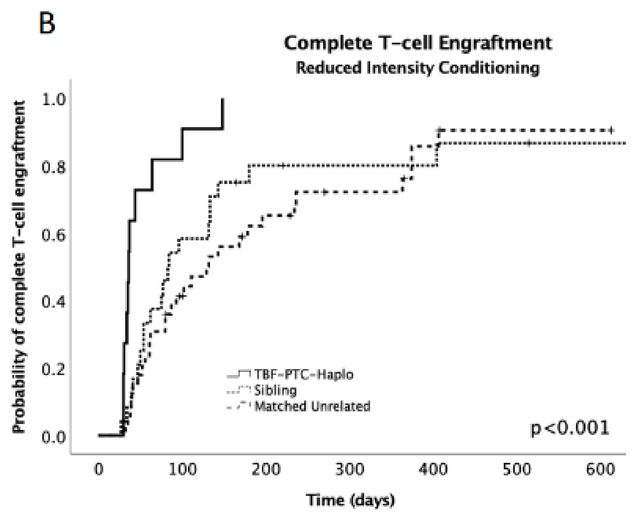

Figure 1B: Kaplan- Meier Curve showing probability of achieving T cell chimerism depending on donor regimen

CONCLUSIONS

The reduced intensity TBF-PCT-based haploidentical regimen results in rapid complete whole blood and T-cell donor chimerism. In this cohort, early complete T-cell chimerism is associated with lower rates of disease relapse.

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