



# Allogeneic Hematopoietic Stem Cell Transplantation at Fifty: Is it Facing an Existential Crisis in the Midst of Newer Innovations in the Field of Hematological Malignancies!

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## Editorial

In the beginning of the 1960s, an obituary for allogeneic Hematopoietic Stem Cell Transplantation (HSCT) was epitaphed with the failure of over 200 documented procedures [1]. The next decade witnessed the silent resurgence of allogeneic HSCT through diligent, methodical and painstaking preclinical studies by E.D. Thomas and his young team [2]. Fifty years later, the veracity of this procedure is being questioned again by every new molecule entering the field of hematological malignancies. Allogeneic HSCT is no longer considered an option for Chronic Myeloid Leukemia (CML) where tyrosine kinase inhibitors provide a long-term survival and even cure in a fraction of patients [3]. Whilst this might seem pertinent in CML, the reason for its exclusion in the treatment algorithm for myeloma remains questionable [4]. In a disease marked by recurrent relapses and progressive decline in quality of life, allogeneic transplantation at a suitable time could undoubtedly cure a significant proportion of such patients. The utility of allogeneic HSCT in Ph positive acute lymphoblastic leukemia is also being scrutinized [5]. A recent explosion of more targeted therapy in acute myeloid leukemia might be raising the same doubts in the minds of critics of allogeneic HSCT.

The concept of cure of cancer through immunological assault on residual cancer cells by donor derived immune cells is the primary goal of allogeneic HSCT for hematological malignancies [6]. Yet, when the procedure was conceived the focus was on escalation of conditioning to eradicate leukemia and merely seed the marrow with healthy donor-derived HSC [7]. It was only in the 1990s, through the works of Kolb, Slavin and others; the primacy of immunological eradication of cancer by an allogeneic graft was established over the intensity of conditioning [8]. The next two decades witnessed the realization of some of the true potential of allogeneic HSCT by offering a stable graft even in the elderly and the frail with minimal conditioning [9]. However, the importance of rigorous HLA matching with the donor made a family donor available to only 20% of the patients and only a small fraction of non-Caucasian patients could obtain a stringently matched unrelated donor from the existing registries. The feasibility of carrying out Umbilical Cord Blood Transplantation (UCBT) with less stringent HLA matching raised the hope for the procedure being available to a wider population. However, lack of such public cord blood banks outside the more developed nations and the early mortality arising from delayed engraftment associated with UCBT made this a less viable proposition than perceived at its inception.

Through the pioneering works of the investigators from Italy and subsequently the Baltimore group in USA, HSCT from a HLA-haploidentical family donor became a reality over the last decade [10,11]. Allogeneic HSCT was at the brink of being at its imperial best, hoping to conquer the frontiers which had remained elusive and untouched. Since the development of small molecules and monoclonal antibodies targeting specific genetic aberrations in cancer, the critics of allogeneic HSCT seem to have found their lost voice once again. Advent of genetic engineering has opened the horizon to newer possibilities of engaging autologous T cells against specific tumor targets, which donor derived T cells have been achieving in the context of an allograft. The much-cursed graft-versus-host disease viewed as an evil twin of graft-versus-tumor effect along with the early

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mortality have been the prime reasons for maligning this procedure born out of decades of painstaking research by the pioneers in this field. The failure to address these problems stem from the fractious immunological perspective of the clinicians and the unpredictability of human response to each facet of allogeneic HSCT. Attempts at attenuating Graft-Versus-Host Disease (GVHD) through T cell depletion is writ with the hazard of delayed immune recovery, resultant opportunistic infections and a compromised GVT effect [12]. The advent of Post-Transplantation Cyclophosphamide (PTCy) has widened the scope of haploidentical HSCT as it is associated with low Non-Relapse Mortality (NRM) and GVHD. However, the outcome of high-risk or advanced leukemia remains compromised due to high incidence of relapse [13].

Chimeric Antigen Receptor (CAR)-T cells on the other hand, the youngest kid in the block, despite producing dramatic responses in refractory B-cell ALL, was associated with unexpectedly high incidence of cytokine release syndrome and unexplained cerebral events [14]. In the excitement of welcoming the new arrivals in the family, the time-tested curative approaches are being ignored. It is premature and naïve to compare an approach which is still in its infancy to one which has stood the rigorous test of time. Rather than positioning newer innovations at odds against allogeneic HSCT, the two approaches could be merged to obtain the best outcomes in dire situations [15].

In the context of haploidentical HSCT, it has been shown that GVT effect can be generated via Natural Killer (NK) cells by abrogating T cell induced alloreactivity without compromising immune recovery through CTLA4Ig primed donor lymphocyte infusions [16]. With extremely low incidence of acute GVHD as well as non-relapse mortality and a survival of 75%, this approach holds the promise to rejuvenate allogeneic HSCT at a time where its position its relevance as upfront option is being challenged due to high NRM and GVHD [17]. Standing at the crossroads of a changing paradigm, allogeneic HSCT needs to reinvent itself through several such innovations where cure is not a trade-off with early mortality or morbidity. The real potential of an allogeneic HSCT remains to be explored and the doomsday prophets might have to eat their words if the basic and clinical researchers in the field can once again rediscover the zeal and commitment of the pioneers in this field.

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