EDITORIAL

Bone Marrow Transplantation for Primary Immune Deficiency Disorders in India: Past, Present and Future

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Primary immune deficiency disorders (PID) are a group of under-diagnosed and under-treated entities [1,2] with high morbidity and mortality. A review of 386 patients of PID from India reported the most common forms to be disorders of immune regulation followed by phagocytic disorders and predominant antibody deficiencies [2]. Bone marrow transplantation (BMT) is a curative option for many PID. Barriers to cure include lack of early diagnosis and referral, lack of diagnostic facilities especially genetic tests, lack of centers specializing in transplant for PID, and high cost of BMT [1].

The number of patients seeking BMT in India has increased over the last five years. Nearly 2000 BMTs,with more than 1000 allogeneic, are being performed annually across 75 centers as per Indian Stem Cell Transplant Registry (ISCTR) 2017 report (personal communication). Pediatric BMT outcomes are also improving. A recent retrospective analysis from eight centers has reported 76% overall survival in 717 children after BMT. Thalassemia (33%) was the commonest indication for BMT whilst PID (2.1%) was the rarest [3]. However, outcome data for BMT in PID is lacking. In this issue of *Indian Pediatrics*, Uppuluri, *et al.* [4] describe largest experience from India – 85 children with PID undergoing BMT with 67% overall survival. This is the right time to describe the journey from a difficult past to a happening present and an exciting future.

Past: BMT for PID in India has made a slow progress. The first case reported was of a child suffering from Wiskott-Aldrich syndrome (WAS) who underwent a successful matched sibling donor (MSD) BMT [5]. A total of 150 children with PID have undergone BMT in last 5 years as per the ISCTR 2017 report. In last decade, alternative donor BMT has been performed for various PIDs. Few landmarks have been – first unrelated cord blood transplant (UCBT) performed for a child with familial hemophagocytic lymphohistiocytosis [6], first haploidentical with post-transplant cyclophosphamide (PTCy) for severe combined immune deficiency (SCID) [7], matched unrelated donor (MUD) BMT and haploidentical BMT with TCR alpha-beta/CD19 depletion for WAS [8].

Present: BMT centers in India have grown from just 10 in 2005 to 75 in 2017. Now alternative donor transplants are being performed for children, especially from half-matched (haploidentical) family donors (mother, father, uncles and aunts) solving problem of donor scarcity [9]. The main highlight of the paper by Uppuruli, *et al.* [4] is the alternative donor transplant, which was performed in 47 out of 85 transplants (MUD-8, UCBT-14 and haploidentical-25). Newer reduced toxicity conditioning regimens using agents like Treosulfan and Fludarabine or Busulfan and Fludarabine with or without Thiotepa and Graft versus host disease (GVHD) regimens like PTCy or TCR alpha-beta/CD19 depletion from the donor graft have made BMT for PID safer [4,8,10]. Another heartening aspect is the spectrum of PID undergoing BMT in India – SCID, WAS and HLH were nearly 67% of total BMT in the present study but many other children with rare PID have also been transplanted [4]. Multi-speciality care, especially good pediatric intensive care support, is needed to improve outcomes as highlighted in the present paper [4]. Mixed chimerism was seen in 20% children in the present study; however, another study from India [10] has shown fully donor chimerism in a series of 8 patients undergoing reduced toxicity BMT with PTCy as GVHD prophylaxis. TCR alpha-beta/CD19 depletion is another new technique that can reduce GVHD rates tremendously with haploidentical donors. In present study, six such transplants were performed and another such BMT has been reported for WAS [8].

Future: Transplant-related mortality remains the major challenge in children with PID undergoing BMT as shown in present study [4]. Another challenge is to reduce long-term sequelae of chemotherapy and/or radiotherapy in these very young children. Chronic GVHD is another unwanted complication that affects quality of life. In

future, transplants would be with minimal or no chemotherapy as it would be replaced by monoclonal antibodies targeting host bone marrow. Another possibility is availability of gene therapy in the near future. After correcting genetic defect (either by lentivirus or by gene editing) in the host bone marrow, it would be re-infused in patient after administering some chemotherapy, and this would be a GVHD-free autologous BMT. *In-utero* stem cell transplantation would be another new possibility. Better supportive care like cytotoxic T-cells specific for viruses and fungi would reduce mortality. Monitoring of drug levels such as busulfan or treosufan can reduce toxicity. Post-transplant donor lymphocyte infusions can help convert mixed chimersim to fully donor. Better drugs for acute and chronic GVHD (*e.g*., ruxotilinib and ibrutinib) might help save lives. Setting up of long-term follow-up clinics would help improve outcomes further.

In conclusion, India is making fast strides in BMT for PID, and in future we should be able to diagnose early and transplant early, and save many more lives with better quality of life.

Funding: None; *Competing interests*: None stated.

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