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Blood and Bone Marrow Transplantation in India: Past, Present, and Future

Prologue – The Global Scenario

Interest in the field of bone marrow transplantation was kindled in the early 1950s when laboratory and clinical experiments had begun in the US and France, triggered by the injury caused by nuclear warfare, during and post-WWII.[1] Animal and laboratory experiments provided proof of the principle.[2] As many patients with marrow aplasia and advanced leukemia had no curative treatment, clinical transplants were done as experimental procedures; however, due to lack of adequate knowledge in transplantation immunology and inadequate supportive care, most of them died either due to relapse, infection, or severe graft-versus-host disease (GVHD).[1,3]

It took conviction of Thomas, first at Cooperstown, then at Fred Hutchison Cancer Research Center (FHCRC), Seattle, to pursue the procedure; better understanding of transplantation immunology through the works of many biologists, specially by Peter Medawar and dog experiments at Seattle, helped to find effective conditioning regimens and GVHD prophylaxis and soon led to a series of successful human allogeneic bone marrow transplants in acute leukemia and severe aplastic anemia.[4] By the late 1970s and early 1980s, the field exploded with many centers performing the procedure across the world.[5] In subsequent years, the indications expanded with autologous transplants for chemosensitive diseases such as lymphomas, myeloma, and some childhood tumors; dearth of matched sibling donors made it necessary to explore matched unrelated donors (MUDs) and umbilical cord blood as sources of hematopoietic stem cells.[6,7] In recent years, the use of haploidentical transplants has shown exponential increment.

Bone Marrow and Blood Stem Cell Transplantation in India

The past (1983–1999)

Keeping in view the international progress and its urgent need in the country, Tata Memorial Centre/Tata Memorial Hospital (TMH) took the lead by sending two young medical oncologists, Dr. S. H. Advani and Dr. R. Gopal in 1981–1982 to FHCRC for training. In March 1983, the first allogeneic bone marrow transplant (BMT) was carried out in a 9-year-old girl with acute myeloid leukemia (AML) in CR1, the donor being a serologically 6/6 antigen-matched younger brother.[8] It was a successful transplant – the recipient survived 22 years without a relapse (GVHD and relapse free), but unfortunately succumbed to uncontrolled diabetes mellitus and tuberculosis. This sad outcome emphasizes the need for awareness, identification, and effective management of long-term complications of the procedure. CMCH, Vellore, soon followed a team ably led by Dr. Mammen Chandy; the hospital began allogeneic BMT in 1986 and in a decade became a center of repute, particularly in the area of thalassemia major and aplastic anemia.[9-11] The Medical Oncology Department at IRCH/AIIMS, New Delhi, led by Dr. Vinod Kochupillai, was the third center to initiate the procedure. It took nearly two decades for the establishment of a few more centers across the country, Indian Stem Cell Transplant Registry/Indian Society for Blood and Marrow Transplantation (ISCTR/ISBMT).

The CMCH team explored the pros and cons of the commonly used BuCy regimens, investigating laboratory parameters of cyclophosphamide and oral busulfan and also clinical toxicities of rejection and hepatotoxicity. Subsequently, they were able to identify a subgroup of very high-risk Stage 3 thalassemia patients.[10] Inclusion of treosulfan in the conditioning regimen appears to have improved outcome in these patients.[12] The TMH team focused on chronic myeloid leukemia until advent of imatinib;[13] we even explored the feasibility of reduced intensity transplants.[14]

An oft-repeated question is, why it took so long for India to expand its transplant program? There are many factors in initial days: (i) lack of trained transplant physicians, (ii) financial, a general hurdle in the field of health care in the country, (iii) lack of support from government agencies, and (iv) private sector health care expanded only toward the later part of last century. Government support is crucial – for countries such as South Korea, Iran, Saudi Arabia, Taiwan, and China; such support played a significant role. Even here, CMCH could develop the program to a higher level after a proposal was approved by the Indian Council of Medical Research.

The present (2000–2020)

The premier institutes mentioned above and a few more in the country were able to train sufficient number of young physicians in the field of BMT/stem cell transplantation (SCT) who went on to start programs in both government and private hospitals, with significant opportunities in the private sector (ISCTR/ISBMT data, personal communication, unpublished). Currently, 97 transplant centers are reporting to the ISBMT (Registry). Only a few have not joined the registry yet. The most recent report from the registry show approximately 19,000

transplants reported as activity data in various indications: allogeneic transplants being preferred by major centers. The main indications are thalassemia major, severe aplastic anemia, acute myeloid leukemia, and acute lymphoblastic leukemia (ALL). In the area of autologous, main indications are multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma in adults, and neuroblastoma in children. As family size has shrunken in India too, demand for MUD increased and currently a number of centers are recognized by the National Marrow Donor Program, DKMS (Deutsche KnochenMarkSpenderdatei or German Bone Marrow Donor File), and others. The DATRI registry is doing an excellent job of finding Indian donors. In addition, the Marrow Donor Registry India, based in Mumbai, is an active registry. However, such donor search is time-consuming, costly, and at times donor attrition leads to heartbreaks. Such events can lead to legal issues. The safety and success of posttransplant cyclophosphamide (PTCy), pioneered by the Johns Hopkins group, has opened up the field of haploidentical transplants for Indian patients. Anyone in the family could be a potential donor.

Repurposing drugs, with a sound rationale, is an important endeavor in treating an autoimmune condition like chronic GVHD. TMH group has taken a lead in this regard by showing effectiveness of leflunomide in certain subsets of patients.[15]

A few words on pediatric population in India who are candidates for BMT will not be out of place; in fact, it needs a special mention. Majority of thalassemia patients are young, usually, below 10 years of age; the number is massive who needs an allogeneic transplants until we find an alternative methods of effective management. The wait list is long in major centers. In recent years, a set of pediatric transplant physicians have taken the onus of looking after these children – a laudable sign. In addition, these physicians along with the nursing team are equipped to perform transplants for immune deficiency diseases.[16] Transplanted children need special care – before, during the procedure, and certainly long-term follow-up. They need a guided rehabilitation program.

The future (2020 to eternity)

It is never easy to see a future – look what happened to Vision 2020! Nonetheless, we notice that the hematopoietic stem cell transplantation (HSCT) activities are peaking in the country. We expect there will be more number of centers becoming active. One region where HSCT has not been initiated yet is North-East India. Patients need to travel outside or continue with nontransplant options within these states. There is little doubt about further expansion of haploidentical transplant program, thus reducing the MUD and umbilical cord transplant numbers. It is difficult to be sure if it is a good direction, but logistic constraints have led to this situation. A word of caution about haploidentical transplants – as a similar strategy utilizing PTCy is being explored in matched sibling donor transplants as well, there is a reduction in GVHD but definitely at the cost of increased risk of opportunistic infections, most noticeably, cytomegalovirus reactivation and possibility of increased relapse.[16] Recent laboratory data point toward multifunctional effects of PTCy on the prevention of alloreactive T cells dysfunction and suppression.[17] Well-designed randomized trials will provide answers.

Application of tyrosine kinase inhibitors (TKIs) and other novel targeted agents is beginning to bring changes in transplant approach.[18] Assessment of measurable minimal residual disease (MRD) has become widely used in ALL, AML, multiple myeloma, and chronic lymphocytic leukemia. MRD negativity following standard therapy appears to be a prerequisite for a better outcome. Hence, use of novel bispecific T cell engager monoclonal antibody like blinatumomab is being increasingly used for achieving MRD negativity before transplantation for B cell ALL.[19] Chimeric antigen receptor (CAR) T cells are helping to treat high-risk or relapsed ALL, thus acting as a bridge, enabling more cases to undergo allogeneic transplants.[20] These modalities are not yet available in the country, but as we have always noted, with passage of time, facilities become available.

Many attempts are being made to improve transplant outcomes in AML. FLT3-positive patients receive upfront FLT 3 inhibitors and continue maintenance.[21] Similarly, hypomethylating agents are being incorporated to maintenance therapy.[22]

In the autologous transplant front, despite advent of novel agents, eligible myeloma cases appear to derive benefit from high-dose melphalan; however, wider applicability of newer monoclonal antibodies and and CAR-T cell therapy might change the algorithm. The practical challenge here will be the unrealistic cost of novel drugs. Following the wider use of rituximab in aggressive lymphomas, outcome of autologous SCT has fallen significantly. These cases are highly chemoresistant, even to myeloablative doses. Recently approved CAR-T cell therapy seems to be highly efficacious, both from response and durability of response point of view.[23,24] Nevertheless, more recent data presented at the transcatheter cardiovascular therapeutics (TCT) 2020 meeting emphasized that CAR-T responses were not durable, thus raising further challenges in managing poor-risk and relapsed/refractory lymphomas.

Will HSCT become redundant one day? A very difficult question to answer in 2020. Nevertheless, as we continue to notice beneficial role of allogeneic transplants for TKI resistant CML, added benefit of high-dose melphalan in multiple myeloma, and its

curative role in relapsed ALL following blinatumomab or CAR-T cell therapy, there is no imminent possibility of HSCT becoming a forgotten modality. Regardless, one wishes that a treatment modality that causes a number of uncalled for iatrogenic conditions becomes redundant one day – time will tell.

Epilogue

As I mentioned, prediction is hazardous; while working on this editorial with procrastination, the pandemic of COVID-19 has appeared and brought the world down. The arena of HSCT has gone for a scramble. Transplant community has been compelled to make many an urgent changes – deferring collection of stem cells, postponing new cases to be admitted unless very high-risk ones, facing serious delay in transportation of MUD cells, not to mention the extra burden of testing cases for possible infections, and finding ways to manage when there are no specific medicines to treat.[25] The economic hardship for patients and health-care institutions and risk of primary disease progression will be realized only in coming days. Prayers are in plenty, in the meanwhile. So much for predictions! But the human resilience and skill shall overcome this hurdle too. A new order will emerge from the ongoing calamity.

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