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Mini Review

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Advances in Hematopoietic Stem Cell Transplantation

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Introduction

Since the first successful allogenic hematopoietic stem cell transplant in 1972 by Dr. Thomas, the technique has gained importance worldwide. It has become potentially curative for many neoplastic and non-malignant disorders. Hematopoietic stem cell transplantation (HSCT) using autologous or allogeneic hematopoietic progenitor cells has progressed and evolved because of the ability to apply new transplant concepts with this therapy, such as cord blood transplantation (CBT) and, more recently, haploidentical donor transplants. These advances have allowed for a broader range of donors. On the other hand, strategies to graft-versus-host disease (GVHD) prophylaxis, is a viable alternative. Many strategies for GVHD prophylaxis are in course in many preclinical or clinical studies. Pitfalls, such as graft rejection, severe GVHD and patient immune suppression are becoming less harmful as the advances in the field progresses.

The Early Days

Since the early beginnings, in the late 1940s, HSCT has become an established care for an increasing number of patients with hematologic malignancies, congenital or acquired disorders of the hematopoietic system and some solid tumors [1-3].

In 1949, Jacobson et al. reported that mice were able to survive from lethal irradiation with the graft of spleen cells from health donors [4]. The X-irradiated animals had the recovery of hematopoiesis after the infusion of spleen cells. Shortly thereafter, Lorenz et al. [5] reported that irradiated mice and guinea pigs injected with health bone marrow cells could reconstitute the hematopoietic system. These researchers thought that the hematopoietic recovery was due by some humoral factor in the spleen or bone marrow [6]. It was hypothesized the following: "evidence strongly suggests that the factor (or factors) responsible for protection from radiation under these circumstances is noncellular and may be required only for the initiation of the repair process. The factor (or factors) may be quite labile or, as is more likely, may be produced in an effective quantity only by living cells" [6]. However, by the mid-1950s, the "humoral hypothesis" was rejected since many publications showed that the radiation protection of the recipient marrow was due to transplanted donor cells hematopoietically function in the host [7-11]. These reports established the cellular hypothesis.

In 1956, Barnes and Loutit reported an approach to treat leukaemia in experimental mice injected with leukemic cells. Mice could be rescued after lethally irradiation-transplantation grafts with health bone marrow donor cells [12]. The authors evoked the extrapolation of the results from mouse to man for the treatment of leukaemia. They introduced the concepts of therapeutic bone marrow transplantation and cell therapy.

The first allogeneic HSCT was tested in 1957 in a pioneering paper by Thomas et al. [13]. They reported six leukemic patients treated with total body irradiation (TBI) and chemotherapy with subsequent intravenous infusion of marrow from a normal donor. Only one patient showed a transient marrow graft. Since little was known about histocompatibility, these trials did not match donors and recipients.

In 1959, the same group described the transplantation of bone marrow cells into two leukemic patients with high-dose TBI [14]. These patients were diagnosed with advanced acute leukaemia and they were conditioned with chemotherapy and TBI and then infused with bone marrow from their homozygous twins (syngeneic transplantation), which led to hematological reconstitution. Although successful transplantation, both patients suffered relapse after a few months. Thomas and co-workers performed the first bone marrow transplantation (BMT) for acute leukaemia patients. This trial gave credibility to the concept that a human syngeneic graft could reconstitute the hematopoietic system and that additional chemotherapeutic protocol to eliminate the leukaemia might be needed.

Soon many bone marrow transplants were performed worldwide. About 200 trials were made between 1959 and 1962; however none of the recipient became long time survivors [15]. It seems that the unsuccessful allogeneic bone marrow transplantations were due to poor histocompatibility typing available, lack of effective supportive care such as antibiotics, lack of transfusional support with platelets and to the TBI protocol that was not so effective to achieve the immunosuppression necessary [1,16-18].

The accumulated experiences with marrow transplantation were very disappointing. Major complications for bone marrow transplants, as graft failure, graft rejection, graft-versus-host disease (GVHD) and death from opportunistic infections resulted in poor transplant outcomes and no patients who were transplanted in the late 1950s and early 1960s survived. Since the first studies of GVHD in mice it was soon correlated its occurrence and the successful of marrow transplantation [9,19,20].

In the late 1960s, methods to identify and type human leukocyte antigens (HLA) in humans were developed [21]. Thereafter, numerous studies elucidated the role of these antigens in HSCT which allowed for donor and recipient HLA matching. In 1972, Thomas et al. in the Seattle Transplantation Group reported the first successful allogeneic transplantation for severe aplastic anaemia [22]. In this work four patients with complete marrow failure were grafted and two patients had an excellent functioning marrow grafts without GVHD. In 1990, Thomas won a Nobel Prize for his work with HSCT.

Establishment of Hematopoietic Cell Transplantation Therapy

The 1980s and 1990s noticed a rapid increase in the number of

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transplants achieved and cord blood was recognized as a source of stem cells. The first cord blood transplant (CBT) was published 1989 in a patient with Fanconi Anaemia (FA) [23]. The FA patient was a boy with severe FA who received the cryopreserved umbilical-cord blood collected at birth from his sister, who was shown to be unaffected by the disease, to have a normal karyotype and to be HLA-identical to the patient. The patient had no GVHD and is currently healthy with a complete long-term hematological and immunological reconstitution [24]. This pioneering work was the result of an intensive collaboration among three groups: AD. Auerbach from the Rockefeller University in New York (USA); Broxmeyer from Indiana University in Indianapolis (USA); and Gluckman from Hospital Saint Louis in Paris (France) [24]. As the result of this work the interest in use of the umbilical cord blood (UCB) as a source of stem cells for unrelated, related, or autologous transplant increased.

The recognition that peripheral blood could be a viable source of hematopoietic stem and progenitor cells opened new possibilities in autologous transplantation [25].

Since peripheral blood stem cells (PBSCs) can be easily mobilized and collected they offer advantages, such as the easy harvest from peripheral blood and more rapid engraftment [26-29].

All these advances paved the foundation of the HSCT in autologous and allogenic grafts. The combined efforts unifying preclinical models and clinical trials resulted in a remarkable progress in the field of HSCT. Advances in conditioning regimens, donor selection, donor registries, tissue typing methods, supportive care, immunosuppression and cooperation of physicians worldwide has resulted in improved patients' long-term survival. HSCT has evolved to an established curative treatment for many congenital or acquired disorders of the hematopoietic system as well as some solid tumors.

The Worldwide Network for Blood and Marrow Transplantation (WBMT) announced a landmark in December 2012: the world's 1 millionth blood stem cell transplant [30]. The finding is based on data collected by WBMT international member organizations engaged in HSCT. The 1,450 transplant centers from 72 countries over 5 continents had reported 1 Million HSCT (58% autologous, 42% allogeneic) [31]. HSCT numbers show continued growth: approximately 70,000 HSCT were performed worldwide in 2012 [32].

However, we still deal with complications resulting from HSCT. Myeloablative conditioning approaches have serious toxicities. Although myeloablative conditioning provides rapid hematopoietic engraftment of donor cells, it also causes myelotoxicity, considerable morbidity and mortality in patients with advanced age or comorbidities [33].

Graft-Versus-Host Disease

GVHD is one of the main complications in allogenic HSCT. Nearly 40-60% of the HSCT recipients develops GVHD with varying degrees of severity and mortality [34] and is fatal to approximately 15% of transplant recipients [35]. The development and severity of GVHD in HSCT recipients may vary on recipient age, conditioning regimen, hematopoietic graft source and GVHD prophylaxis [36].

Based on the time frame, pathogenesis, symptoms and organ involvement GVHD can be characterized as acute or chronic GVHD [37]. Acute GVHD (aGVHD) occurs most frequently after engraftment, arising before day 100 post-transplant. However, this arbitrary period of 100 days, has become imprecise due to the development of an acute GVHD beyond day 100 after graft. It has been estimated that, 30-50% of all transplanted patients will experience acute GVHD and results for 15% of post-transplantation mortality [38,39]. Chronic GVHD (cGVHD) occurs beyond 100 days of the HSCT and is a common complication of allogeneic graft. cGVHD occurs in 40% of HLA identical sibling HSCT, more than 50% of HLA- non-identical related HSCT and in 70% of matched unrelated HSCT patients [40,41]. It is the major cause of nonrelapse morbidity and mortality in allogeneic HSCT recipients and a major obstacle to improving outcomes. Despite the progress in understanding the pathophysiology of GVHD, the restricted success of therapies for prevention and treatment of GVHD are still unsatisfactory. In Grade I aGVHD, affecting only the skin, topical steroids alone are often used, while more advanced grades require systemic therapy with high dose methylprednisolone. In cGVHD first line systemic treatment is orally administered prednisolone and cyclosporine are used, but patients who are steroid-refractory have a poor outcome, with long-term mortality rates that can achieve 90% [35,41].

Prevention of GVHD

Despite the progress in understanding the pathophysiology of GVHD has considerably improved in the last few years, the limited success of established therapies for prevention of GVHD remains a challenge. The use of intensive conditioning regimens and, high doses of TBI induces a greater risk of GVHD due to the tissue damage, which represents the first phase of the pathophysiology of aGVHD [42]. Prevention strategies have been directed at reducing aGVHD, which is the mainly significant risk factor for the development of cGVHD [43].

T cell depletion prophylaxis for GVHD was started in the 1980s. It is an effective mean of prevention of GVHD. However, this can be counterpoise by the increased risk of delayed immune reconstitution, graft failure and disease recurrence [44].

Immunosuppressive therapy is an important tool for the prevention of aGVHD. Early studies demonstrated the advantage of a combination of cyclosporine, with methotrexate over methotrexate alone. This combination remains the most frequently used method of prophylaxis [41]. Since methotrexate has toxic effects, such as increased time to hematopoietic engraftment, neutropenia, mucositis and organ toxicities, some investigators introduced a protocol using the mycophenolate mofetil (MMF) combined with cyclosporine [45].

Human mesenchymal stromal/stem cells (MSCs) are defined as self-renewing, multipotent progenitor cells with multilineage potential. MSCs have been shown to have immunomodulatory properties with anti-inflammatory, anti-proliferative, immunosuppressive abilities and also low immunogenicity, which may make them useful for transplantation [46]. Le Blanc et al. firstly reported that bone marrow-derived MSCs rescued a pediatric patient experiencing grade IV refractory aGVHD [47]. Several studies suggest that MSCs are effective to treat aGVHD [48-52]. In experimental models MSCs modulate immune system through several mechanisms, including suppression of $CD4^+$ and $CD8^+$ T cell proliferation, induction of regulatory T cells, suppression of B cell differentiation and proliferation, release of soluble immunomodulatory factors and repair of damaged target organs [53-57]. However, little is known about MSCs effects on patients with GVHD. As this field progresses, studies with MSCs will be important to determine the mechanism of its immunomodulatory properties in patients with GVHD.

Conclusion

Despite advances achieved in HSCT, the GVHD remains

a remarkable obstacle to successful allogeneic transplantation. Developing safer strategies to prevent and treat GVHD will expand the HSCT to higher-risk transplant populations, such as elderly patients and those with higher co-morbidities or advanced diseases.

With studies in experimental models the pathogenesis of GVHD has radically improved and has led to new therapeutic possibilities. Efforts to prevent and treat GVHD have been more successful in the last 10 years, primarily though improvements in graft sources and GVHD prophylaxis.

Alternatively, development of novel transplantation protocols with co-infusion with MSCs should improve seeding capacity of donor MSCs to rapidly replenish damaged host niche-forming cells and to employ their unique immunosuppressive properties. Because GVHD is a common cause of non-relapse morbidity and mortality the positive effects of MSC therapy will have great value in a HSCT. However, there are still some obstacles to overcome: i) The standardization process of MSCs production in different transplantation centers, ii) Optimization of the cell infusion, frequency and interval of administration.

These clearly demonstrate that the field of HSCT is changing rapidly with new therapeutic possibilities and inclusion of new cell therapy technologies. The success of HSCT in the next future will be the conjunction of therapeutic strategies. Further the scientific investigation is leading to the discovery of effective strategies for HSCT as a more efficient therapy.

References

1. Appelbaum FR (2007) Hematopoietic-cell transplantation at 50. N Engl J Med 357: 1472-1475.
2. Müller AM, Huppertz S, Henschler R (2016) Hematopoietic stem cells in regenerative medicine: Astray or on the Path? Transfus Med Hemother 43: 247-254.
3. Passweg JR, Baldomero H, Peters C, Gaspar HB, Cesaro S, et al. (2014) Hematopoietic SCT in Europe: Data and trends in 2012 with special consideration of pediatric transplantation. Bone Marrow Transplant 49: 744-750.
4. Jacobson LO, Marks EK, Robson M, Zirkle RE (1949) The effect of spleen protection on mortality following x-irradiation. J Lab Clin Med 34: 1538-1543.
5. Lorenz E, Uphoff D, Reid TR, Shelton E (1951) Modification of irradiation injury in mice and guinea pigs by bone marrow injections. J Natl Cancer Inst 12: 197-201.
6. Jacobson LO (1952) Evidence for a humoral factor (or factors) concerned in recovery from radiation injury: A review. Cancer Res 12:315-325.
7. Barnes DWH, Loutit JF (1954) What is the recovery factor in spleen. Nucleonics 12: 68-71.
8. Main JM, Prehn TR (1955) Successful skin homografts after the administration of high dosage X radiation and homologous bone marrow. J Nat Cancer Inst 15: 1023-1029.
9. Trentin JJ (1956) Mortality and skin transplantability in X-Irradiated mice receiving isologous, homologous or heterologous bone marrow. Exp Biol Med 92: 688-693.
10. Ford CE, Hamerton JL, Barnes DW, Loutit JF (1956) Cytological identification of radiation-chimaeras. Nature 177: 452-454.
11. Nowell PC, Cole LJ, Habermeyer JG, Roan PL (1956) Growth and continued function of rat marrow cells in X-radiated mice. Cancer Res 16: 258-261.
12. Barnes DWH, Loutit JF (1957) Treatment of murine leukaemia with x rays and homologous bone marrow. British Med J 2: 626-627.
13. Thomas ED, Lochte HL JR, LU WC, Ferrebee JW (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 257: 491-496.
14. Thomas ED, Lochte HL Jr, Cannon JH, Sahler OD, Ferrebee JW (1959) Supralethal whole body irradiation and isologous marrow transplantation in man. J Clin Invest 38: 1709-1716.
15. Bortin MM (1970) A compendium of reported human bone marrow transplants. Transplantation 9: 571-587.
16. Little MT, Storb R (2002) History of haematopoietic stem-cell transplantation. Nat Rev Cancer 2: 231-238.
17. Juric MK, Ghimire S, Ogonek J, Weissinger EM, Holler E, et al. (2016) Milestones of hematopoietic stem cell transplantation-from first human studies to current developments. Front Immunol 7: 470.
18. Ezzone SA (2009) History of hematopoietic stem cell transplantation. Semin Oncol Nurs 25: 95-99.
19. Schwartz EE, Upton AC, Congdon CC (1957) A fatal reaction caused by implantation of adult parental spleen tissue in irradiated F1 mice. Exp Biol Med 96: 797-800.
20. Billingham RE (1958) Studies on the reaction of injected homologous lymphoid tissue cells against the host. Ann N Y Acad Sci 73: 782-788.
21. van Rood JJ (1968) The detection of transplantation antigens in leukocytes. Seminars in Hematol 5: 187-214.
22. Thomas ED, Storb R, Fefer A, Slichter SJ, Bryant JI, et al. (1972) Aplastic anaemia treated by marrow transplantation. Lancet 1: 284-289.
23. Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, et al. (1989) Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med 321: 1174-1178.
24. Gluckman E (2009) History of cord blood transplantation. Bone Marrow Transplant 44: 621-626.
25. Juttner CA, To LB, Ho JQ, Bardy PG, Dyson PG, et al. (1988) Early lympho-hemopoietic recovery after autografting using peripheral blood stem cells in acute non-lymphoblastic leukaemia. Transplant Proc 20: 40-42.
26. Gianni A, Siena S, Bregni M, Tarella C, Stern AC, et al. (1989) Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for auto transplantation. The Lancet 334: 580-585.
27. Bensinger W, Clift RA, Anasetti C, Appelbaum FA, Demirer T, et al. (1995) Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 85: 1655-1658.
28. Körbling M, Champlin R (1996) Peripheral blood progenitor cell transplantation: A replacement for marrow auto- or allo-grafts. Stem Cells 14: 185-195.
29. Mohty M, Ho MD (2011) In and out of the niche: Perspectives in mobilization of hematopoietic stem cells. Exp Hematol 39: 723-729.
30. Keating A, DaSilva G, Pérez WS, Gupta V, Cutler CS, et al. (2013) Autologous blood cell transplantation versus HLA-identical sibling transplantation for acute myeloid leukemia in first complete remission: A registry study from the Center for International Blood and Marrow Transplantation Research. Haematologica 98: 185-192.
31. WBMT (2013) 1 millionth blood stem cell transplant marks major medical milestone. WBMT.
32. Dietger N, Marcelo CP, Mahmoud DA, Dennis LC, Helen B, et al. (2013) Global hematopoietic stem cell transplantation (HSCT) at one million: An achievement of pioneers and foreseeable challenges for the next decade. A report from the worldwide network for blood and marrow transplantation (WBMT). Blood 122: 2133-2133.
33. Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, et al. (2016) Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the worldwide network for blood and marrow transplantation group including the global survey. Bone Marrow Transplantation 51: 778-785.
34. Gratwohl A, Carreras E (2012) Principles of conditioning in the EBMT-ESH handbook on haematopoietic stem cell transplantation. The European Society for Blood and Marrow Transplantation, pp: 123-137.
35. Choi SW, Reddy P (2014) Current and emerging strategies for the prevention of graft-versus-host disease. Nat Rev Clin Oncol 11: 536-547.
36. Blazar BR, Murphy WJ, Abedi M (2012) Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 12: 443-458.

37. Villa N, Rahman MM, McFadden G, Cogle CR (2016) Therapeutics for graft-versus-host disease: From conventional therapies to novel virotherapeutic strategies. Viruses 8: 85.

38. Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373: 1550-1561.

39. Ball LM, Egeler RM (2008) Acute GvHD: Pathogenesis and classification. Bone Marrow Transplant 41: S58-S64.

40. Qian L, Wu Z, Shen J (2013) Advances in the treatment of acute graft-versus-host disease. J Cell Mol Med 17: 966-975.

41. Lee SJ, Flowers ME (2008) Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program.

42. Apperley J, Masszi T (2012) Graft-versus-host disease in the EBMT-ESH handbook on haematopoietic stem cell transplantation. Eur Soc for Blood and Marrow Transplant.

43. Messina C, Faraci M, de Fazio V, Dini G, Calò MP, et al. (2008) Prevention and treatment of acute GvHD. Bone Marrow Transplant 41: S65-S70.

44. Lee SJ, Vogelsang G, Flowers ME (2003) Chronic graft-versus-host disease. Biol Blood Marrow Transplant 9: 215-233.

45. Ho VT, Soiffer RJ (2001) The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation. Blood 98: 3192-3204.

46. Bolwell B, Sobecks R, Pohlman B, Andresen S, Rybicki L, et al. (2004) A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. Bone Marrow Transplant 34: 621-625.

47. Ozaki K, Sato K, Oh I, Meguro A, Tatara R, et al. (2007) Mechanisms of immunomodulation by mesenchymal stem cells. Int J Hematol 86: 5-7.

48. Le Blanc K, Rasmusson I, Sundberg B, Götherström C, Hassan M, et al. (2004) Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 363: 1439-1441.

49. Zhao K, Lou R, Huang F, Peng Y, Jiang Z, et al. (2015) Immunomodulation effects of mesenchymal stromal cells on acute graft-versus-host disease after hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation 21: 97-104.

50. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, et al. (2008) Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 371: 1579-1586.

51. Kurtzberg J, Prockop S, Teira P, Bittencourt H, Lewis V, et al. (2014) Allogeneic human mesenchymal stem cell therapy (remestemcel-L, Prochymal) as a rescue agent for severe refractory acute graft-versus-host disease in pediatric patients. Biol Blood Marrow Transplant 20: 229-235.

52. Ringden O, Le Blanc K (2011) Mesenchymal stem cells for treatment of acute and chronic graft-versus-host disease, tissue toxicity and hemorrhages. Best Prac Res Clin Haematol 24: 65-72.

53. von Dalowski F, Kramer M, Wermke M, Wehner R, Röllig C, et al. (2016) Mesenchymal stromal cells for treatment of acute steroid-refractory graft versus host disease: Clinical responses and long-term outcome. Stem Cells 34: 357-366.

54. Zhao S, Wehner R, Bornhäuser M, Wassmuth R, Bachmann M, et al. (2009) Immunomodulatory properties of mesenchymal stromal cells and their therapeutic consequences for immune-mediated disorders. Stem Cells and Dev 19: 607-614.

55. Fernández-García M, Yañez RM, Sánchez-Domínguez R, Hernando-Rodriguez M, Peces-Barba M, et al. (2015) Mesenchymal stromal cells enhance the engraftment of hematopoietic stem cells in an autologous mouse transplantation model. Stem Cell Res Ther 6: 1-13.

56. Lopez-Santalla M, Mancheño-Corvo P, Menta R, Lopez-Belmonte J, DelaRosa O, et al. (2015) Human adipose-derived mesenchymal stem cells modulate experimental autoimmune arthritis by modifying early adaptive T cell responses. Stem Cells 33: 3493-3503.

57. Chen L, Tredget EE, Liu C, Wu Y (2009) Analysis of allogenicity of mesenchymal stem cells in engraftment and wound healing in mice. PLoS ONE 4: e7119.

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