JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Bone Marrow and Stem Cell Research

Perspective

The Double Face of Janus: A Historical Account of the Emergence of Bone Marrow Transplantation

Camilla Scanlan[*1], Ian Kerridge [1, 2]

[1] *Centre for Values, Ethics & the Law in Medicine, University of Sydney NSW, Australia*

[2] *Department of Hematology, Royal North Shore Hospital, St Leonards, NSW, Australia*

Corresponding author: Dr. Camilla Scanlan, Centre for Values, Ethics & the Law in Medicine, University of Sydney NSW, 2006, Australia, Tel: 61(0)413 963 738; Email: Camilla.scanlan@sydney.edu.au

Received: 02-16-2016

Accepted: 02-24-2016

Published: 03-04-2016

Abstract

History of modern blood and marrow transplantation (BMT) emerged, as is the case with most new biomedical interventions from sustained clinical and scientific research. But BMT also has a much darker antecedent – nuclear power and chemical warfare.

It is important that we know the full story of the emergence of BMT for two reasons. The first is that it illustrates how accounts of the history of medicine in terms of heroes and beneficent progress are simplistic and often erroneous. The second is that it reminds us that biomedical knowledge may arise from human misery and may also cause it.

Keywords: Bone Marrow Transplantation, BMT; Hematopoiesis; Histocompatibility; Ionizing Radiation; Chemical Warfare; History of Medicine

Abbreviations:

BMT: Bone Marrow Transplantation;

HSCT: Hematopoeitic Stem Cell Transplant

Introduction

The history of bone marrow transplantation is a rich and interesting account. It has its beginnings around the time of World War II, and was founded in concerns about the biological consequences of atomic warfare [1]. As a result, much of the early research into the effects of exposure to ionizing radiation and the possibility of hematopoietic 'rescue' was conducted under the auspices of various Departments of Defense and was not published until many years later [2].

Knowledge of the Effects of Ionizing Radiation

During the 1940s and 50s Leon Jacobson [3], in a series of elegantly designed experiments conducted at the University of Chicago, described the sensitivity of the hematopoietic system to ionizing radiation. Jacobson demonstrated that mice exposed to radiation in doses sufficient to destroy the hematopoietic cells in the bone marrow, did not die when the spleen (the organ of hematopoiesis in the mouse) was shielded from the direct effects of radiation, suggesting that death following exposure to radiation was due, at least in part, to failure of the hematopoietic system. In subsequent studies, Jacobson and colleagues exposed another cohort of mice to total body irradiation (TBI), but followed this, in some of the mice, with an intraperitoneal injection of cells derived from the spleen. When those mice that had received the splenic cells survived, Jacobson concluded that these mice had essentially been 'rescued from death' (a term that continues to be used in the 21st century) by the re-establishment of hematopoiesis.

The Importance of 'likeness' between Donor and Recipient

Concurrent with this research, Lorenz and colleagues [4] had shown that guinea pigs exposed to lethal doses of radiotherapy could be kept alive if they were injected/infused with hematopoietic cells taken from the bone marrow of a genetically identical littermate. This research built upon the work of the Nobel Laureate Alexis Carrel in the early 1900s that showed that cells or organs transplanted from one individual (donor) to another (recipient), would be recognized by the recipient as being 'foreign' if the pair were not genetically identical – with graft rejection occurring following nonidentical transplantation but not after syngeneic transplantation (ie between monozygotic twins) [5,6]. (A process subsequently demonstrated by Doherty and Zinkernagel to be mediated by a dense clustering of genes associated with the major histocompatibility complex (MHC) [7].)

As the immune system and the immunobiology of transplantation became better understood, over the following decades increasing attention was devoted to the need to immunologically 'match' donors to recipients who were not genetically identical. While this led to some success – with many irradiated-then-infused allogeneic recipients remaining free of malignancy – many also developed severe diarrhea, weight loss, and skin lesions – a constellation of signs and symptoms that Balner and colleagues termed 'secondary disease', but which is now know as graft-versus-host disease (GvHD) [8].

This early research had therefore shown that hematopoietic tissue destroyed by irradiation, could be replaced and repopulated by infusing a suspension of hematopoietic cells derived from a healthy donor. The survival and proliferation of such grafts occurred, not as a consequence of a humoral response, as had been postulated by Jacobson [9], but as Ford et al identified [10] because [a] the infused cell suspension colonized the vacant spaces in the bone marrow of the recipient, taking over the role of producing blood cells and [b] the body, as a result of the irradiation, failed to recognize the infused cells as foreign, and destroy them by the elaboration of antibodies produced against them i.e. by an immunogenic response.

From the start – this new knowledge was recognized as having implications not only for the military, (Ford was funded by the British Atomic Energy Research Establishment, and Jacobson by the USA's Atomic Energy Commission) but in clinical settings – opening up the possibility of curing patients with radiosensitive malignant disease, particularly hematological malignancies, by the purposeful destruction of their malignant cells with radiotherapy (and subsequently chemotherapy), followed by the infusion of healthy marrow cells.

The First Successful Bone Marrow Transplant in Humans

Although the American physician Robert A Good is often believed to have performed the first successful bone marrow transplant in 1968 [11] the first 'successful' bone marrow transplant had actually occurred almost a decade earlier. On October 15 1958, six persons were exposed to high doses of neutrons and gamma radiation during an accident at a nuclear research reactor at Vinca in former Yugoslavia (now known as Serbia and Montenegro). All six individuals were flown to the Hôpital Curie in Paris under the care of oncologist Georges Mathé. Initially they were treated for severe radiation sickness with transfusions of whole blood, packed red blood cells, concentrated platelets, γ-globulin, and antibiotics, but they did not show any signs of clinical improvement. On the 27th day after the accident, a suspension of human adult bone marrow cells was infused intravenously to five of the six patients (the man not transplanted having received a sub-lethal dose of radiation). Each transplanted patient's condition improved, however one of the men died shortly thereafter as a result of radiation damage to the viscera. Four of the five transplanted victims survived [12,13]. Notwithstanding, whilst Mathé's BMTs likely contributed to the survival of the 5 workers

who developed radiation sickness, until Good and his team successfully transplanted a 5-month old boy with Severe Combined Immunodeficiency (SCID) with bone marrow from his 8-year old sister, all of the more than 200 attempts to transplant bone marrow in humans had led to the death of the recipients [14].

Elsewhere in the United States, researchers were exploring the immunological basis of transplantation and graft rejection. E Donnall Thomas, in particular, was one of the first to recognize the impact of genetic match between donor and recipient on graft and recipient survival. Thomas, who was later to receive the Nobel Prize for Physiology and Medicine for his work, his wife Dottie and their team, began applying insights drawn from experiments on dogs to advancing unrelated donor BMT in human trials in the 1960s. (Prior to this all successful BMTs had been between genetically identical siblings.) [15] Finally, in 1969, after years of work on developing an understanding of, and the means of detecting the effects of immunological differences between donor and recipient (histocompatibility) by assays (tissue typing) and development of antibiotics that inhibit transplant infections, Thomas performed the first successful unrelated allogeneic bone marrow transplant in humans [16] – work that was to form the basis for the expansion of BMT throughout the world and to the foundation of the Fred Hutchinson Cancer Research Centre in Seattle.

The differences between the transplants performed by Mathé and Thomas are worthy of note because they illustrate how much had been achieved during the decade that separated their work. The transplants done by Mathé were performed under emergency conditions; exposure to radiation had been accidental and the doses were uncontrolled – being variously described as supra-lethal, lethal and sub-lethal; the donor and recipients had been matched on sex and major blood groups only; and the intention was to 'rescue' patients from the effects of an industrial radiation exposure [17]. In contrast, in Thomas' patients the doses of radiation administered were controlled and calculated on body mass; donors had been matched to recipients using tissue typing to the level of complexity as was known at the time; and the intention was cure an underlying hematological malignancy.

Adjunct Therapy

The subsequent development of bone marrow transplantation as a clinical therapy owes much to the development of chemotherapy [18]. The use of chemotherapy (a term coined by the German chemist Paul Ehrlich) to treat cancer, rather than infection, was prompted by knowledge derived from experiences with chemical warfare and, more specifically, with the use of mustard gas in World War I. Initial studies done in 1943, but not published until much later [19], revealed that soldiers who had come into contact with mustard gas experienced high rates of bleeding (both internally and externally) and were highly susceptible to infections. Subsequent reports revealed that men exposed to mustard gas during World War II had bone marrow failure and that this was the cause of much of its toxicity. Drawing from these insights it was reasoned that if chemicals could affect normal hematopoietic cells then they might also affect rapidly growing malignant cells [20]. To test this hypothesis, nitrogen mustard was used to treat patients with lymphoma, often with some initial success, although remissions turned out to be brief and incomplete, leading many researchers to believe that cancer was not curable by drugs.

Progress in understanding the roles of both radiotherapy and chemotherapy in treating patients with various malignancies advanced significantly during the following decades. Early research conducted in the 1960s [21-25] demonstrated that the ability of these agents to kill tumor cells was directly related to the doses given to the patient - the higher the dose, the better the 'kill rate' – leading to intensification of radiation and/or chemotherapy doses in the hope that this may increase cure and reduce the likelihood of post-BMT relapse. While this strategy was, in many situations, successful, it also resulted in greater toxicity to normal tissue, in particular the gastrointestinal tract, the renal, hepatic, pulmonary, liver and cardiac systems, causing much of the mortality and morbidity associated with BMT [26].

More recently, a range of strategies have been pursued with the intention of reducing the toxic effects of radiation and/or chemotherapy and optimising not only the likelihood of post-BMT survival but the *quality* of post-BMT survival. These strategies have included the use of 'reduced intensity' transplant conditioning protocols, increasingly sophisticated approaches to tissue-typing, better supportive care and the exploration of immunotherapy rather than pharmacotherapy to treat both malignancy and infection. Collectively, progress in these areas will likely increase the number of patients eligible for BMT and outcomes following BMT.

Conclusion

BMT is now clearly established as standard treatment for a wide variety of life-threatening diseases affecting both children and adults and provides long-term disease free survival in up to 80% of patients. While it is often tempting to read the scientific and clinical emergence of medical therapies, like BMT, as a story of inexorable and beneficent progress, of the brave triumph of medical science over disease, in fact medical advance is rarely so simple and often results from serendipitous findings or after long periods of fruitless or misguided study. And in some situations, such as with BMT, medical advance arises in the context of human misery or following the pursuit of science for militaristic purposes. While this does not invalidate or even sully the benefits that accrue from BMT it should give us pause

to acknowledge the capacity of science, and knowledge more generally, to reduce but also to cause suffering.

Camilla Scanlan,	AAIMS, BSc, MBA, MHL, PhD(Med)
Ian Kerridge,	BA, BMed(Hons), MPhil, FRCPA, FRACP
Funding Statement	*The authors received no direct funding relevant to this article*
Conflict of Interests Declaration	*The authors declare no conflict of interests*
Acknowledgments	None

References

1. Teal GE, Fabrizio RA, Barnes SM, Moeller WA. Training Requirements For Postattack Adaptive Behaviour. Final Report1965. Report No.: AD-624870

2. Gilman AG. Therapeutic applications of chemical warfare agents. Fed Proc. 1946 Jun1946 5:285-92.

3. Jacobson LO. Evidence for a humoral factor (or factors) concerned in recovery from radiation injury: A review. Cancer Res. 1952, 12(5): 315-325.

4. Lorenz E, Uphoff D, Reid T, Shelton E. Modification of acute irradiation injury in mice and guinea pigs by bone marrow injection. Radiology. 1951, 58(6): 863-877.

5. Akerman J. Alexis Carrel: Nobel Prize for physiology and medicine.1912. Transplant Proc. 1987, 19(4Suppl 5): 9-11.

6. Baron F, Storb R, Little M-T. Hematopoietic cell transplantation: five decades of progress. Arch Med Res. 2003, 34(6): 528-544.

7. Doherty P, Zinkernagel R. A biological role for the major histocompatibility antigens. The Lancet. 1975, 305(7922): 1406-1409.

8. Balner H, De Vries MJ, Van Bekkum DW. Secondary disease in rat radiation chimeras. J Natl Cancer Inst. 1964, 32.

9. Jacobson LO. Evidence for a Humoral Factor (or Factors) Concerned in Recovery from Radiation Injury: A Review. Cancer Research. 1952,12(5): 315-325.

10. Ford C, Hamerton J, Barnes D, Loutit J. Cytological identification of radiation-chimeras Nature. 1956, 177(4506): 452-454.

11. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. The Lancet. 1968, 292(7583): 1366-1369.

12. Van Bekkum D, de Vries J. Radiation Chimeras. In: Atkinson K, editor. Clinical Bone Marrow and Blood Stem Cell Transplantation. 2nd ed. London: Logos Press Ltd; 1969, 259-277.

13. Jansen J. The first successful allogeneic bone-marrow transplant: Georges Mathe. Transfusion medicine reviews. 2005, 19(3): 246-248.

14. Bortin MM. A compendium of reported human bone marrow transplants. Transplantation. 1970, 9(6): 571-587.

15. Thomas ED, Lochte HL, Cannon JH, Sahler OD, Ferrebee JW. Supralethal Wholed Body Irradiation and Isologous Marrow Transplantation in Man. J Clin Invest. 1959, 38((10 Pt 1-2)): 1709-1716.

16. Thomas ED, Buckner CD, Rudolph RH, Fefer A, Storb R et al. Allogeneic marrow grafting for hematologic malignancy using HL-A matched donor-recipient sibling pairs. Blood.1971, 38(3): 267.

17. LeadingArticle. Survival of Bone Marrow Grafts. BMJ. 1960, 1: 1189-1191.

18. DeVita VT, Chu E. A History of Cancer Chemotherapy Cancer Res. 2008, 68(21): 8643-8653.

19. Gilman AG. Therapeutic applications of chemical warfare agents. Fed Proc. 1946, 5: 285-292.

20. Marshall Jr EK. HistoricaI Perspectives In Chemotherapy. In: Golding A, Hawking I, editors. Advances in chemotherapy. New York: New York: Academic Press.1964, 1-8.

21. Hewitt HB, Wilson CW. A survival curve for mammalian leukemia cells irradiated *in vivo* (implications for the treatment of mouse leukemia by whole-body irradiation). Br J Cancer. 1959, 13: 69-75.

22. Bush RS, Bruce WR. The radiation sensitivity of transplanted lymphoma cells as determined by the spleen colony method. Radiat Res. 1964, 21(4): 612-621.

23. Bruce WA, Meeker BE, Valeriote FA. Comparison of the sensitivity of normal hematopoietic and transplanted lymphoma colony-forming cells to chemotherapeutic agents administered *in vivo.* J Natl Cancer Inst. 1966, 32: 233-245.

24. Goldin A. Factors pertaining to complete drug-induced remission of tumor in animals and man. Cancer Res. 1969, 29(12): 2285-2291.

25. Skipper HE, Schmidt LH. A manual on quantitative drug evaluation in experimental tumor systems. Cancer Chemother Rep. 1962, 17: 1-143.

26. Apperley JF, Bacigalupo A, Friedrich W, Girinsky T, Goldstone AH et al. Principles of Conditioning Regime. In: Apperley J, Gluckman E, Gratwohl A, Craddock CF, editors. Blood and Marow Transplantation. Paris2000.