Perspective

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

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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: Hematopoietic 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...
that soldiers who had come into contact with 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.

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