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Historical markers in the development of allogeneic hematopoietic cell transplantation

E. Donnall Thomas,[1] *Karl G. Blume*[2]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; [2]Division of Bone Marrow Transplantation, Stanford University Medical School, Stanford, California

Correspondence: E. Donnall Thomas, MD, Professor of Medicine, Emeritus, Member, University of Washington, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N. D5-100, Seattle, WA 98109

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INTRODUCTION

As we come to the close of the second millenium, it is interesting to note that almost everything we know about the transplantation of tissues and organs has come about in the 20th century. Alexis Carrel received the Nobel Prize in medicine in 1912 for his work on vascular sutures and the transplantation of blood vessels and organs. He and others showed that an allogeneic graft could function for a time but then would fail. The antigenic basis of tumor transplants was established based on experiments in mice[1] and led to the recognition of the H2 transplantation antigen system [2]. Medawar clearly established the immunologic basis for graft rejection and described neonatal tolerance in mice [3]. Thus, at the end of World War II, the stage was set for the development of hematopoietic cell transplantation.

This brief account of historical markers is intended to highlight those publications that had a direct bearing on the clinical application of hematopoietic cell transplantation. Three excellent monographs provide detailed information about the development of transplantation biology [4–6].

1949–1951: THE HUMORAL HYPOTHESIS

During this time, because of the possibility of atomic warfare and the newly available radioactive isotopes, there was a great deal of interest in the biological effects of irradiation. It was recognized that the bone marrow was the most sensitive organ in the body and that marrow failure was the cause of death at low lethal radiation exposures. In 1949, Jacobson *et al.* found that mice could survive an otherwise lethal irradiation exposure if the spleen were protected by a lead foil [7]. In 1951, Lorenz *et al.* described a similar protective effect of an infusion of spleen or marrow cells [8]. It was logical to think that the marrow recovery was the consequence of humoral or hormonal factors that stimulated the marrow regrowth and, thus, allowed the mice to survive.

1954–1956: THE CELLULAR HYPOTHESIS

In 1954, Barnes and Loutit noted that the recovery brought about by spleen or marrow cell infusion might be due to living cells and that the reported experiments did not exclude the cellular hypothesis [9]. In 1955, Main and Prehn described studies of lethally irradiated mice protected by a marrow infusion and given subsequent skin grafts from the marrow donor [10]. Even across major histocompatibility barriers, donor skin grafts were not rejected, a proof of tolerance that could be explained only by the transfer of living cells. In 1956, Ford *et al.* showed that the marrow of such mice displayed the cytogenetic characteristics of the marrow donor [11].

1956–1959: RECOGNITION OF THE POTENTIAL OF MARROW GRAFTING IN THE TREATMENT OF HUMAN DISEASE

In 1956, Barnes *et al.* described the treatment of murine leukemia by supralethal irradiation and marrow grafting [12]. They pointed out the potential application of marrow grafting to human patients. Attempts to treat human patients by supralethal irradiation and marrow grafting were reported by Thomas *et al.* in 1957 [13]. In 1958, Kurnick *et al.* described the use of the patients' own marrow to facilitate marrow recovery of patients with solid tumors treated intensively with chemo-irradiation [14]. In 1959, Thomas *et al.* reported two patients with advanced leukemia who were treated with supralethal irradiation and marrow from their identical twins. Although their leukemia came back in a few months, they

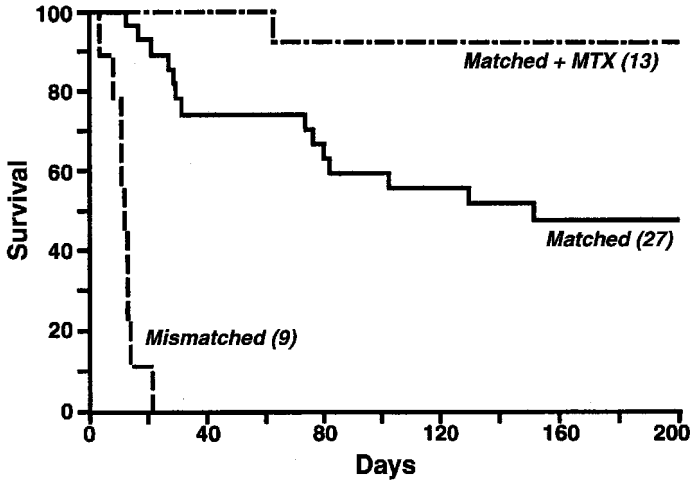

Figure 1. Outcome in dogs after transplantation following irradiation

Survival of dogs given 1000 rad total body irradiation and marrow from littermates matched and mismatched for dog leukocyte antigens. Some recipients of matched marrow were given a short course of intermittent methotrexate after grafting to suppress the GVH reaction (adapted from [31–33]).

were the first patients deliberately given supralethal irradiation, and their prompt hematological recovery supported the principles underlying this new treatment strategy [15].

1956–1959: ADVANCES IN MARROW GRAFTING TECHNOLOGY THROUGH ANIMAL STUDIES

Experiments in inbred mice defined the immunology of allogeneic grafting. It was shown in mice that intravenous infusion was the optimal route for administration of marrow stem cells [16]. Bellingham and Brent found that allogeneic cells in the marrow graft could mount an immune reaction against the tissue of the host, resulting in a wasting syndrome now known as graft-vs.-host disease (GVHD) [17]. Uphoff reported that genetic factors controlled the immune reactions of donor cells against the host [18] and that methotrexate could ameliorate the graft-vs.-host reaction [19].

Following the Main and Prehn report described above and its confirmation by other researchers, there was a great deal of interest in the possibility that a marrow graft followed by an organ graft might be a general method for allogeneic transplantation in mammalian species. In 1959, Mannick *et al.* described a dog given lethal irradiation and a marrow graft, followed by a kidney transplant, from an unrelated dog [20]. The treated dog died of pneumonia 73 days after irradiation and 49 days after the kidney graft, with a cellular marrow and no sign of rejection of the kidney. This animal illustrated proof that marrow graft followed by organ graft could be successful, but, unfortunately, demonstrated the hazards of allogeneic marrow grafting. This approach to allogeneic organ transplantation was abandoned because of similar disasters in human patients and also because immunosuppressive drugs were beginning to be introduced at that time.

1960–1967: PESSIMISM ABOUT ALLOGENEIC MARROW GRAFTING IN HUMAN PATIENTS BUT PROGRESS IN ANIMAL MODELS OF ALLOGENEIC MARROW GRAFTING

Bortin collected data about approximately 200 human allogeneic marrow grafts carried out in the 1950s and 1960s and concluded that none had been successful [21]. Mathé *et al.* achieved the first allogeneic marrow graft in a patient with leukemia, but the patient died with many problems that probably were due to the complications of chronic GVHD [22]. Continued success with transplantation between identical twins demonstrated the feasibility of marrow grafting between histocompatible donors and recipients.

Dogs are an outbred species suitable for clinical procedures used for human patients, and family groups of them are readily available. It was found that dogs could survive 2 to 4 times the lethal exposure to irradiation if given an intravenous infusion of their own marrow cells that had been set aside or cryopreserved before the irradiation [23,24]. Studies in dogs demonstrated the spectrum of results following allogeneic marrow grafting, including failure of engraftment, graft rejection, engraftment followed by GVHD, and stable engraftment without GVHD [25]. Hematopoietic cells for engraftment could be obtained from the peripheral blood in dogs as well as in mice [26,27].

Dausset *et al.* and van Rood *et al.* had described human leukocyte antigen (HLA) groups [28,29], and it was thought that these antigens might be important in transplantation. Studies of skin graft survival in human volunteers suggested that the human leukocyte antigens were histocompatibility antigens, but the graft survivals were difficult to interpret and the technique carried the risk of transmission of disease to and sensitization of the recipient [30].

Studies of the dog leukocyte antigen system proved that dog leukocyte antigens (DLA) were crucial in determining the outcome of an allogeneic marrow graft [31]. Dogs given irradiation and marrow from a DLA-mismatched littermate died of graft rejection or GVHD. Most recipients of DLA-matched marrow, especially those given some postgrafting methotrexate to suppress the GVH reaction, became long-term healthy survivors [32–34] (Fig. 1). These observations encouraged further trials of marrow grafting between matched human siblings.

1968–1975: THE BEGINNING OF THE MODERN ERA OF HUMAN MARROW TRANSPLANTATION

Effective supportive care of the patient without marrow function had been developed by 1968, including blood component transfusion technology and improved antibiotics. Increasing knowledge of HLA systems made it possible to select compatible family members as marrow donors. In 1968 and 1969, three infants with immune deficiency diseases received successful transplants from HLA-matched siblings [35–37]. Because of their disease, these patients required neither immunosuppression to prevent rejection and GVHD nor cytotoxic agents to eliminate malignancy. More than 25 years later, these three patients are well and are leading normal lives.

Successful marrow grafts from matched siblings proved to be much more difficult to achieve for older children and adults with advanced leukemia or aplastic anemia. In 1969, the Seattle team treated a patient with the blastic phase of chronic myeloid leukemia by total body irradiation and marrow transplantation from a matched sibling. The transplantation was successful, but the patient died of cytomegalovirus pneumonia, an early example of the problem of opportunistic infections in the postgrafting period [38].

In 1972, the Seattle team reported successful transplantations for patients with severe aplastic anemia [39]. In 1975, a review article by members of the team described the state of knowledge of marrow transplantation at that time [40]. The article described the results in 37 patients with severe aplastic anemia and 73 with leukemia in the terminal phase of their disease who received transplants after failure of conventional treatment. Notable results were successful engraftment of some patients with aplastic anemia, and engraftment and survival in remission of a few patients with leukemia.

1976–1986: WIDENING APPLICATION OF ALLOGENEIC MARROW GRAFTING FOR HUMAN PATIENTS

In 1976, the Seattle team reported the development of a plateau on a semilog plot of a Kaplan-Meier disease-free survival curve, suggesting that some patients with advanced leukemia were being cured by chemo-irradiation and marrow grafting [4l]. In 1977, they reported the long-term survival of 13 of 100 patients who received transplants for advanced leukemia [42].

Once it was shown that some patients in the end stages of leukemia could be cured, it became possible to consider transplantations earlier in the course of the disease. In 1979, two reports of transplantation for acute myeloid leukemia in first remission showed greatly improved results [43,44].

Chronic myeloid leukemia (CML) had not been cured by chemotherapy, but in 1979, Fefer *et al.* described the disappearance of the Ph chromosome in four patients treated with chemotherapy, irradiation, and an identical twin marrow transplant [45]. Preliminary reports had described treatment of CML in chronic phase by chemo-irradiation and allogeneic marrow transplantation from a matched sibling [46,47]. In 1986, two studies of large numbers of patients with CML reported that a majority could be cured by chemo-irradiation and a marrow graft [48,49]. Figure 2 shows the clinical results of 389 patients with CML who received marrow grafts from histocompatible related donors.

The first cures of Thalassemia major and of sickle cell disease were also reported during this period [50,51]. Figure 3 illustrates the outcome of transplantation for 34 patients with sickle cell anemia. Better prevention and control of GVHD came from removal of T cells from the marrow innoculum [52,53] or by a combination of a short course of methotrexate combined with cyclosporine [54,55].

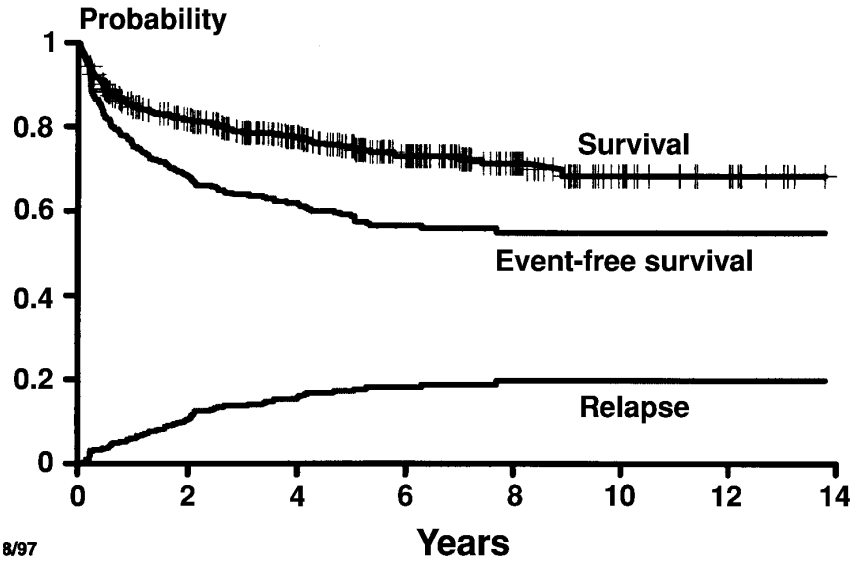

Figure 2. Patient outcome after transplantation for CML

Kaplan-Meier estimates for survival, event-free survival, and cumulative incidence of relapse through 1996 for 389 patients in Seattle with CML who received transplants from HLA-identical related donors during the chronic phase after treatment with either cyclophosphamide with total body irradiation or busulfan with cyclophosphamide (reproduced by permission from Thomas ED and Cliff RA: Allogeneic transplantation for chronic myeloid leukemia. In: ED Thomas, KG Blume, SJ Forman [eds] Hematopoietic Cell Transplantation. 2nd ed. Boston: Blackwell Science, 811, 1999).

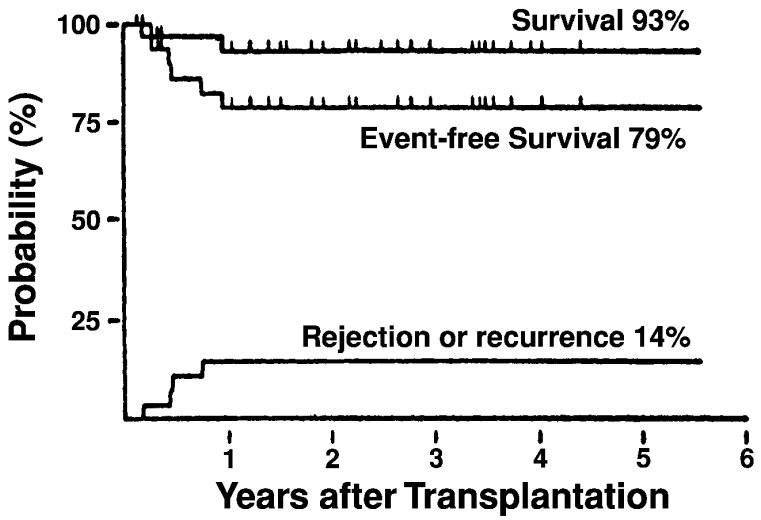

Figure 3. Patient outcome after transplantation for sickle cell disease

Kaplan-Meier estimates for survival and event-free survival following marrow transplantation for sickle cell disease are shown. An event is defined as death, graft rejection, or recurrence of sickle cell disease. A cumulative incidence curve for rejection and return of sickle cell disease is also depicted (reproduced by permission from Walters MC, Patience M, Leisenring W, et al. Collaborative multi-center investigation of marrow transplantation for sickle cell disease: current results and future directions. Biol Blood Marrow Transplant 3:310, 1997).

1986–PRESENT: HEMATOPOIETIC CELL TRANSPLANTATION AS STANDARD THERAPY

With hundreds of marrow transplant teams reporting data, it is not possible to cite all the important publications in the space available. Among the most notable are the following:

- The development of the preparative regimen of cyclophosphamide and busulfan that avoids the use of irradiation for some diseases [56].
- The introduction of ganciclovir for the control of cytomegalovirus infections [57,58] (reviewed in [59]).
- The use of donor lymphocyte infusions for eradication of recurrent leukemia or lymphoproliferative disease [60–62].
- The use of hematopoietic stem cells from peripheral blood or cord blood, which has changed the terminology from marrow transplantation to hematopoietic cell transplantation [63–65] .
- The advances in immunogenetics of HLA, especially typing by molecular techniques (reviewed in [66]).
- The creation of large panels of tissue-typed volunteer donors that has made possible transplantations from donors who are not family members [67,68]. Donor registries have been established in many countries to facilitate international cooperation in locating matched marrow donors (reviewed in [69]).
- Hematopoietic cell transplantation using nonmyeloablative techniques to avoid regimen-related toxicity and death [70] (reviewed in [7l]). These techniques suggest the feasibility of using hematopoietic cell transplantation as a treatment for autoimmune diseases and preparation for solid organ grafts.
- Successful crossing of the HLA barrier, allowing allogeneic hematopoietic cell transplantation from haplotype-matched related donors [72–74]. The report by Guinan *et al.* opens a new approach to the transplantation of histoincompatible marrow allografts, using cells made anergic by elimination of costimulatory signals [75].

CONCLUSION

During the second half of the 20th century, several generations of investigators from many countries have contributed a wealth of scientific information based on experimental and clinical research. These efforts have changed the role of hematopoietic cell transplantation from a desperate therapeutic maneuver to a curative treatment modality for thousands of patients, especially when it is used for patients in the early stages of their disease. The number of diseases for which hematopoietic cell transplantation can be applied is also increasing rapidly. During the next decades, we are likely to witness a continued gain of new research information, leading to novel and improved concepts that may further extend the application of this form of treatment.

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