



## Nonmyeloablative stem cell transplantation using lymphoablative rather than myeloablative conditioning in the prefludarabine era by ATG and limiting doses of cyclophosphamide

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### Summary:

The feasibility of using lymphoablative rather than myeloablative conditioning for durable engraftment of allogeneic stem cells and subsequent cell therapy with donor lymphocytes was pioneered in the prefludarabine era in patients with resistant lymphoma and metastatic solid tumors. Between July 1995 and August 1996, 15 patients, five males and 10 females, median age 50 (range 20–57) years, were enrolled in a protocol that consisted of different doses of cyclophosphamide (Cy), 50 mg/kg/day for 1, 2, 3 or 4 consecutive days in parallel with a fixed dose of rabbit antithymocyte globulin (ATG) (Fresenius) 10 mg/kg/day for 4 consecutive days. All patients, except one treated with a single dose of Cy, achieved full tri-lineage engraftment and no late graft failure was observed. Only three patients suffered from grade III–IV graft-versus-host disease (GVHD). Three patients out of the 15 survived long term (follow-up >93 to >96 months). We concluded that lymphoablative conditioning with ATG and intermediate-to-high-dose Cy is well tolerated and can result in durable engraftment with acceptable GVHD in heavily pretreated patients with advanced malignancies. Hence, induction of tolerance to donor alloantigens by lymphoablative conditioning while avoiding myeloablative chemotherapy or radiation therapy may serve as a platform for subsequent cell therapy with donor lymphocytes.

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**Keywords:** stem cell transplantation; cyclophosphamide; antithymocyte globulin; reduced-intensity conditioning; nonmyeloablative stem cell transplantation; graft-versus-tumor effects

Animal studies during the 1960s have shown that cyclophosphamide (Cy) can be used as a good immunosuppressive agent to facilitate durable and stable engraftment of allogeneic hematopoietic cells.<sup>1–3</sup> These results led to the introduction of Cy into clinical practice for prevention of rejection of bone marrow allografts in the 1970s.<sup>4,5</sup> Use of high-dose Cy for the treatment of severe aplastic anemia (SAA), where myeloablation was not indicated, held great promise for hematopoietic reconstitution of patients with severe pancytopenia, but rejection remained a major obstacle in previously transfused recipients.<sup>6,7</sup> Storb and colleagues demonstrated that the use of antithymocyte globulin (ATG) in addition to Cy could be effective in overcoming pretransplant sensitization of patients with SAA.<sup>8,9</sup> However, the lymphoablative protocol, based on combining Cy and ATG, was considered effective exclusively for stem cell transplantation (SCT) of patients with severe marrow aplasia.<sup>10–12</sup> Documentation of the role of donor lymphocyte infusion (DLI) in early 1987 by Slavin *et al.*,<sup>13</sup> by Kolb *et al.*<sup>14</sup> and subsequently by other investigators<sup>15,16</sup> suggested that once transplantation tolerance is accomplished by engraftment of donor stem cells, donor lymphocytes rather than myeloablative conditioning by chemoradiotherapy can play an important role in the elimination of malignant or otherwise abnormal host hematopoietic cells. It was reasoned that the use of nonmyeloablative conditioning for stem cell transplantation (NST) could reduce dramatically transplant-related toxicity and early mortality,<sup>17</sup> thus possibly providing high-risk and heavily pretreated patients with cancer or life-threatening nonmalignant disorders with poor performance status a realistic chance to benefit from allogeneic cell-mediated immunotherapy subsequent to allogeneic SCT.<sup>17</sup> Since Cy is a known antilymphocytic alkylating agent that could also be effective against lymphoma and rapidly proliferating cancer cells, it seemed reasonable and justified at the time, prior to the fludarabine era, to attempt induction of durable engraftment of donor stem cells with lymphoablative rather than myeloablative conditioning with different doses of Cy combined with ATG in eligible patients with no alternative modalities. In the present study, we report our first experience, applying ATG and different doses of Cy as the first attempt for intentional nonmyeloablative

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# Nonmyeloablative Stem Cell Transplantation New Frontiers In Cancer Therapy S

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## **Nonmyeloablative Stem Cell Transplantation New Frontiers In Cancer Therapy S:**

**Hematopoietic Stem Cell Transplantation Research Advances** Karl B. Neumann, 2008 Hematopoietic stem cell transplantation HSCT is the transplantation of blood stem cells derived from the bone marrow that is bone marrow transplantation or blood Stem cell transplantation is a medical procedure in the fields of haematology and oncology most often performed for people with diseases of the blood bone marrow or certain types of cancer Stem cell transplantation was pioneered using bone marrow derived stem cells by a team at the Fred Hutchinson Cancer Research Center from the 1950s through the 1970s led by E Donnall Thomas whose work was later recognised with a Nobel Prize in Physiology and Medicine Thomas work showed that bone marrow cells infused intravenously could repopulate the bone marrow and produce new blood cells His work also reduced the likelihood of developing a life threatening complication called Graft versus host disease With the availability of the stem cell growth factors GM-CSF and G-CSF most hematopoietic stem cell transplantation procedures are now performed using stem cells collected from the peripheral blood rather than from the bone marrow Collecting stem cells provides a bigger graft and does not require that the donor be subjected to general anaesthesia to collect the graft Hematopoietic stem cell transplantation remains a risky procedure with many possible complications it has always been reserved for patients with life threatening diseases This book presents recent leading research in the field

*The Embryo* Shraga Blazer, Etan Z. Zimmer, 2005 Sophisticated imaging devices and new biological technologies have greatly enhanced our ability to detect an ever increasing number of fetal malformations during pregnancy Elucidation of the human genetic code and exact molecular definition of various diseases together with enhanced capabilities for repairing genetic defects have opened possibilities for diagnosis and treatment which less than a decade ago could only have been dreamed of However many clinical topics related to the embryo and human genetics as well as the issues of cloning and the use of human embryonic stem cells have outpaced our ability to keep up appropriate public discourse of ethical religious and legal issues This book is designed to bridge the gap between scientific innovation treating clinicians and parents in whose unborn child a malformation was detected and who face a difficult and confusing decision making process All chapters were written by leading authorities and reflect the state of the art as well as the authors personal experiences unique perspectives and predictions for developments in their fields in the near future Specialists in obstetrics gynecology and reproductive medicine pediatrics and neonatology genetics molecular biology philosophy ethics and law will benefit from this book written by international experts in their fields

Standardization of Quality of Life Core Outcomes in Stem Cell Clinical Trials Dori A. Naerbo, 2018-07-16 Background Establishing standardized Quality of Life QOL core outcomes in stem cell clinical trials is important to ensure 1 researchers and clinicians can make informed decisions and 2 clinical trials use and consistently measure the same units Clarke 2007 Thornley Adams 1998 This study reviews the most common QOL methodologies timing frequency of the measurement and outcomes in cardiovascular stem cell clinical trials Methods To identify instruments the

study reviewed MEDLINE Scopus and US Clinical Trials Register through September 2010 and randomized BMSC controlled trials of clinical trials from 2000 2011 The trials all used the terms bone marrow stem cell AND quality of life OR heart OR cardiac AND cardiac AND quality of life OR QOL The study included a Likert scale web based questionnaire comprised of eight questions designed to assess QOL patient satisfaction post cardiovascular stem cell treatment Results Of the instruments identified the study found that bone marrow stem cell BMSC clinical trials used 35 different types of methodologies whereas cardiovascular BMSC employed more consistent methodologies Timing frequency and baseline were consistently measured in BMSC clinical trials whereas cardiovascular BMSC lacked baseline consistency and were measured primarily after treatment Cardiovascular BMSC outcomes were consistent whereas BMSC clinical trials had multiple outcomes The mean participant age was 56 25 years with a minimum age of 46 years and a maximum age of 61 years Participants generally were educated with a minimum education level of an Associate degree and a maximum degree of Doctorate The patient satisfaction survey revealed that participants preferred yes no questions and surveys that required less than 15 minutes to complete received via email easy to understand not too personal relevant to feelings containing a baseline measure and medical condition specific Conclusion QOL outcomes are rarely assessed in BMSC cardiovascular trials Treatments are performed all over the world and no one knows whether these treatments actually are effective Both standardized measurements and additional studies are needed

#### **Pulmonary and Critical Care Considerations of**

**Hematopoietic Stem Cell Transplantation** Ayman O. Soubani, 2023-06-14 This book serves as a guide to the pulmonary and critical care complications of hematopoietic stem cell transplantation HSCT HSCT is an important therapeutic modality for a variety of malignant and non malignant conditions The outcomes of these patients have been improving and the number of HSCT cases is increasing around the world These patients however continue to have post transplant complications related to conditioning regimens and graft vs host disease Pulmonary complications following HSCT remain a major cause of morbidity and mortality in this patient population The book begins with an overview of HSCT and graft vs host disease Chapters then cover particular complications including immunological changes in lungs diffuse alveolar hemorrhage bronchiolitis obliterans and pulmonary fibrosis Other complications including neurologic renal gastrointestinal and cardiac are covered Chapters are comprehensive and consistent with each defining the scope of the complication epidemiology risk factors diagnostic approach management outcome and predictors of outcome and future directions The book provides insight as well on matters that arise during the care of HSCT patients such as provider burnout nursing care intensive care unit organization nutritional support and pulmonary and physical rehabilitation This is an ideal guide for pulmonologists critical care physicians transplant specialists oncologists and relevant trainees caring for patients who have undergone HSCT

**Constructing new motifs in hematology** Erden Atilla, Mutlu Arat, Gunhan Gurman, 2023-06-29 *NK Cell-Based Cancer Immunotherapy* Francisco Borrego, Susana Larrucea, Rafael Solana, Raquel Tarazona, 2016-09-08 Natural killer NK

cells are innate lymphoid cells that have a significant role in regulating the defenses against cancer development and certain viral infections. They are equipped with an array of activating and inhibitory receptors that stimulate or diminish NK cell activity respectively. Inhibitory receptors include among others the MHC class I ligands killer cell immunoglobulin like receptors KIR in humans and members of the Ly49 family of receptors in mice and CD94 NKG2A. Activating receptors include cytokine and chemokine receptors and those that interact with ligands expressed on target cells such as the natural cytotoxicity receptors or NCRs NKp30 NKp44 and NKp46 NKG2D CD244 and DNAM 1. In addition NK cells express Fc RIIIA or CD16 the receptor that exerts antibody dependent cell mediated cytotoxicity ADCC. NK cells also express the death ligands FasL and TRAIL. The killing or sparing of target cells depends on the integration of distinct signals that originate from NK cell receptors. NK cells spare healthy cells that express normal levels of MHC class I molecules and low amounts of stress induced self molecules whereas they kill target cells that down regulate MHC class I molecules and/or up regulate stress induced self molecules. The latter are common signatures of virus infected cells and tumors. All the accumulated knowledge on NK cell biology along with many clinical observations is driving multiple efforts to improve the arsenal of NK cell based therapeutic tools in the fight against malignant diseases. Indeed NK cell based immunotherapy is becoming a promising approach for the treatment of many cancers. It is well known that NK cells have a significant role in the anti tumor effect of therapeutic antibodies that use ADCC as a mechanism of action. In addition to this administration of autologous and allogeneic NK cells after activation and expansion ex vivo is used in the treatment of cancer. Moreover adoptive transfer of NK cell lines has been tested in humans and genetically modified NK cells expressing chimeric antigen receptors are being studied in preclinical models for potential use in the clinic.

**Non-myeloablative Stem Cell Transplantation** Sergio Giralt, Shimon Slavin, 2000

**Cancer Research**, 2005-11 *Basics of Hematopoietic Stem Cell Transplant* Sanjeev Kumar Sharma, 2023-07-24 This book is a quick guide on the hematopoietic stem cell transplant SCT also called bone marrow transplant BMT an evolving field of hematology and hemato oncology. This book covers the various types of stem cell transplants like autologous and allogeneic stem cell transplants indications ways of doing a transplant and stem cell transplants basic principles. Written in a question answer format readers will find it more interesting as one question sequentially leads to another. This book explains the complications of SCT in individual chapters along with the biology of T cells which are the most important cells involved in the success of SCT. This book is beneficial to the budding hematologists oncologists and postgraduates interested in SCT and helps students in their exams. The book would be helpful for readers globally as SCT is a procedure done worldwide and is an ever increasing field for treating various benign and malignant hematological diseases.

**Index Medicus**, 2004 Vols for 1963 include as pt 2 of the Jan issue Medical subject headings **Application of Adult Stem Cells in Regenerative Medicine** Farshid Sefat, Morvarid Saeinasab, 2025-06-03 Application of Adult Stem Cells in Regenerative Medicine offers a comprehensive overview of tissue engineering using adult stem cells to treat various disorders throughout the human body.

The book introduces readers to adult stem cells tissue engineering and their application in regenerative medicine It covers many new and up to date techniques providing a solid foundation for understanding the field Written by global leaders this resource is invaluable for anyone studying researching or working in the areas of adult stem cells tissue engineering or regenerative medicine The book is divided into three parts Part One provides an introduction to adult stem cells and their application in regenerative medicine Part Two focuses on different body organ systems including the nervous respiratory digestive urinary circulatory endocrine skeletal reproductive muscular and ocular systems Part Three concludes with a review of the future of adult stem cells in regenerative medicine This structure ensures that readers gain a thorough understanding of the current state and future potential of adult stem cells in treating various disorders Provides extensive application of adult stems cells in tissue engineering and regenerative medicine Presents various examples of adult stem cells for different organs within the human body Discusses the latest innovations in adult stem cells

*Stem Cell Research* Nancy E. Snow,2003 This volume brings together essays by an internationally distinguished and diverse group of scholars Contributors thoughtfully explore the ethical public policy and scientific implications of embryonic and adult stem cell research Part one of the book offers a variety of scientific and public policy perspectives including essays on stem cell plasticity and using umbilical cord blood as an alternative source of pluripotent stem cells Part two vigorously examines the ethics of stem cell research and considers issues of social justice morality and public policy Scientific alternatives a natural law perspective regarding federal funding and a discussion of the possible moral complicity of Catholic researchers are among the distinctive contributions made to the stem cell research debate by this collection The objective and balanced discussions contained in this volume serve as an accessible introduction to the bioethical questions issues and problems surrounding stem cell research

The Immunotherapeutic Potential of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Andrea Bacigalupo,Charles Craddock,Nicolaus Martin Kröger,2022-02-28

*Everyday Miracles* Burt,Dr. Richard Burt,2023-01-10 Describes the author s approach to treating such incurable diseases as multiple sclerosis and scleroderma using hematopoeitic stem cell transplantation detailing the history of his patients who have found success with the treatment

*New Insights on Liver Transplant and Tolerance* Xiao-Kang Li,Ye Htun Oo,2021-11-24

**Cutting-Edge Translational Research in Graft-Versus-Host Disease (GVHD) and Graft-Versus-Tumor (GVT) Effect After Allogeneic Hematopoietic Cell Transplantation** Tomomi Toubai,Robert Zeiser,2022-07-04

HTLV-1: Addressing Unmet Research Needs Louis M. Mansky,Wei Zhang,2021-05-20

**Cumulated Index Medicus** ,1999

**Total marrow irradiation** Susanta Kumar Hui,Guy Storme,Jeffrey Wong,Monzr M. Al Malki,Bulent Aydogan,2023-07-26

**Oxford Textbook of Cancer in Children** Hubert N. Caron,Andrea Biondi,Tom Boterberg,François Doz,2020-10-08 The outcome for children with cancer has shown enormous improvement since the first edition of this book was published in 1975 In economically privileged countries overall survival rates have now reached 80% at five years from diagnosis and most of these young people

will become long term survivors The Oxford Textbook of Cancer in Children offers state of the art descriptions of the approach needed for the optimal management of children with cancer and guidance on current treatments available due to the advances made over the past decade This seventh edition has been thoroughly revised and updated including brand new chapters on cancer immunotherapy in children and cancer in adolescents and young adults plus expanded treatment of tumours of the brain and central nervous system The book primarily provides clear and up to date clinical guidance for use in treatment settings whilst offering a useful background to the biology of individual tumour types and the history of the development of specific treatments With an international and multi disciplined authorship comprising of paediatric oncologists surgeons radiotherapists imaging specialists psychologists nurses and many others the text illustrates how the paediatric oncology community works globally and collaboratively in order to drive forward new therapies build our knowledge of these diseases and achieve the common aim of curing childhood cancer In this new edition Professors Biondi and Caron have been joined by Professor Francois Doz who has a distinguished international reputation particularly in the treatment of childhood brain tumours and retinoblastoma as well as early drug development They have also been joined by Professor Tom Boterberg a world renowned radio oncologist for children with cancer This book will be of value to paediatric oncologists trainee paediatric oncologists paediatric haematologists and other professionals working in paediatric oncology nurses AHPs surgeons and clinical oncologists

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