Hematopoietic Growth Factors in Transfusion Medicine and Cellular Therapy – Part I

Peter Schlenke a  Andreas Humpe b

a Institute for Transfusion Medicine and Transplantation Immunology, University Hospital Münster, b Division of Stem Cell Transplantation and Immunotherapy, Second Department of Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Germany

On September 12, 1957 E. Donnall Thomas and colleagues reported in the New England Journal of Medicine [1] on their paradigm shift in the treatment of leukemia by applying intravenous infusion of bone marrow after irradiation and chemotherapy. This was the hour of birth of allogeneic stem cell transplantation which is based on the idea to replace malignant transformed bone marrow by healthy bone marrow of another individual. Graft rejection, graft-versus-host disease, leukemic progression, and life-threatening opportunistic infections were the major reasons that none the patients survived longer than 100 days, and great pessimism predominated in the scientific world.

As recapitulated by Frederick R. Appelbaum [2] on the occasion of the 50th anniversary of allogeneic stem cell transplantation Thomas was convinced that donor selection was the key to overcome the assumed incompatibility. The discovery of the dog and human leukocyte antigen system (DLA, HLA) were milestones to learn more about the impact of genetic polymorphisms, to investigate the cause of graft-versus-host disease, and to deal carefully with the donor T-cell-related alloreactivity in respect to initial eradication of residual tumor cells and immunosurveillance thereafter. ‘After all the disappointments of clinical marrow transplants in the late 1950s and early 1960s, there was general pessimism about the field and many of the early investigators moved on to other studies. Nevertheless, improvement in transfusion medicine, the treatment of infections and especially an improved understanding of the importance of HLA typing encouraged a renewed attack on the clinical application of marrow grafts’, summarized Thomas his pioneering work [3].

Nowadays, about 50,000 autologous and allogeneic stem cell transplantations (related/unrelated) per year are performed worldwide in more than 500 transplantation centers [2]. This success story is strongly linked to the special topic of this issue of TRANSFUSION MEDICINE AND HEMOTHERAPY, that is to say the discovery and use of hematopoietic growth factors in transfusion medicine and cellular therapy and their pharmaceutical manufacturing. For example, mouse G-CSF was first purified by Metcalf’s group at the Walter and Eliza Hall Institute in Australia in 1983 [4], whereas the human molecule was cloned by two independent groups in Japan [5] and USA [6] in 1986. Notably, granulocyte colony-stimulating factor (G-CSF) stimulates the amplification of hematopoietic stem cells and myeloid progenitor cells in the bone marrow compartment and facilitates their transendothelial migration into the bloodstream. This phenomenon is not only advantageous for patients with severe chemotherapy-related neutropenia in order to maintain their immune competence against foreign pathogens, but also of paramount importance for collecting sufficient doses of hematopoietic stem cells or neutrophils from the peripheral blood.

Therefore, the introduction of G-CSF for stem cell mobilization revolutionized the practicability of both autologous and allogeneic transplantations. Meanwhile, more than two decades of experiences are on hand to legitimize the use in healthy volunteers after informed consent. The non-inferiority of peripheral blood stem cells in comparison with bone marrow from unrelated donors was recently demonstrated by Anasetti et al. [7] for the Blood and Marrow Transplant Clinical Trials Network. In the current issue, two contributions from the Department of Internal Medicine I at the Technical University of Dresden deal with the risk-benefit assessment of G-CSF in healthy individuals donating either stem cells or granulocytes [8, 9].

It is well known that in a minority, of patients, and – with some other implications – also in very few volunteer donors,
stem cells are not mobilized into the circulation sufficiently. In an autologous setting, these ‘poor’ mobilizers are at risk not to be transplanted unless multiple procedures allow for the collection of at least a single transplant dose or another alternative becomes attractive such as the use of an additional drug with a different mode of action then G-CSF. Plerixafor is such a drug that helps to mobilize hematopoietic stem cells from the bone marrow into the bloodstream by antagonizing the CX chemokine receptor 4 (CXCR4) and its interaction with stromal derived factor 1 (SDF1). Plerixafor is approved by US Food and Drug Administration (FDA) to be used in combination with G-CSF for patients with multiple myeloma and non-Hodgkin’s lymphoma. The physiology and pharmacology of plerixafor is illustrated in a comprehensive review written by S. Fricker, Sanofi-Genzyme [10], whereas the current clinical indications after the European marketing authorization took place in 2009 are summarized by S. Fruehauf [11]. Humpe et al. [11] have added a paper with original data of 14 poor mobilizers who underwent large-volume apheresis after plerixafor supplementation.

The incredible progress in hematopoietic stem cell transplantation has been made possible by recent advances and new avenues in fields such as basic research in stem cell biology (long-term engraftment), growth factor-driven lineage cell fate, collection of mobilized stem cells via leukapheresis, sophisticated graft manipulation techniques (T-cell deple- tion), high-resolution HLA typing, and the charitable recruit- ment of millions of unrelated volunteer donors. The dream will become true that every patient will have at least one suitable donor, including those with a non-perfect tissue match who allow for alternative transplantation options by using cord blood (double or ex vivo expanded) or haploidal-identical donors such as the patient’s parents.

References