

training in hematopoiesis and bone marrow physiology as well as cellular immunology. Encouraged by Prof. Erslev, I even completed a master's program in protein science at Temple University in my second fellowship year. Later, to better understand stem-cell biology, he arranged for me to work for a time at the Toronto Cancer Center, where Prof. Ernest McCulloch and Prof. James Till—who, in their 1961 publications, identified hematopoietic stem cells in mice—were based. All these experiences greatly helped me learn the fundamental principles of hematology in depth., Türkiye Together with my wife, Prof. Tülay Kansu, we completed our postgraduate training in Philadelphia between 1972 and 1980. During my years in Philadelphia, I had the opportunity to meet and work with many distinguished hematologists who made very significant contributions to the field. Prof. Peter C. Nowell of the University of Pennsylvania (who identified the Philadelphia chromosome), Prof. Sol Sherry of Temple University in the field of coagulation, Prof. Sandy Shapiro in anti-phospholipid syndrome and Prof. James Holland the founder of CALGB, among many other esteemed hematologists. Through these collaborations, I gained highly valuable academic knowledge and experience from pioneers of the field., Türkiye Over the last 50 years, hematology has seen major scientific advances that have improved patients' quality of life and expanded treatment options. Among these are the development of cell-culture and genetic technologies; stem-cell transplantation; cancer immunotherapy and targeted therapies; checkpoint inhibitors; gene therapy; biotechnology; innovations in the treatment of sickle-cell disease and thalassemia and advances in imaging and diagnostic methods. In conclusion, I believe that the hematology subspecialty—which I chose with determination and affection in the final years of my internal medicine residency—has made very important contributions to my academic life. I sincerely recommend that our young colleagues choose hematology in their subspecialty training and academic careers.

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Abstract 043

DONOR SELECTION IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapeutic option for various malignant and non-malignant hematological disorders. Donor selection remains the most critical factor affecting transplantation outcomes, with human leukocyte antigen (HLA) compatibility being the cornerstone of this process. The traditional donor hierarchy begins with HLA-matched sibling donors (MSD), who provide the best outcomes with the lowest risk of graft-versus-host disease (GVHD) and transplant-related mortality (TRM). For patients without an MSD, matched unrelated donors (MUD) with 10/10 HLA compatibility are the next preferred option.

Recent advances in high-resolution HLA typing have improved outcomes with unrelated donors, approaching results comparable to those of MSD. When multiple compatible donors are available, non-HLA factors guide selection. Donor age significantly impacts outcomes, with younger donors (18-35 years) yielding better results. Cytomegalovirus serostatus concordance between donor and recipient is crucial to prevent post-transplant complications. Male donors are generally preferred over female donors, particularly for male recipients, due to the increased risk of chronic GVHD associated with female-to-male transplants. ABO blood group compatibility, while not affecting survival directly, influences the risk of immediate post-transplant complications. Alternative donor sources have expanded transplantation possibilities for patients lacking conventional donors. Haploidentical family donors have seen remarkable improvements in outcomes with the introduction of post-transplant cyclophosphamide (PTCy), challenging the traditional donor hierarchy. Umbilical cord blood units provide another alternative, particularly beneficial in pediatric patients, despite limitations in cell dose. Donor selection strategies differ between pediatric and adult populations. In pediatric patients, the focus remains on minimizing long-term complications, particularly chronic GVHD, which can severely impact growth and development. In adults, stronger graft-versus-leukemia effects may be prioritized in high-risk malignancies, making alternative donors with potential for enhanced alloreactivity more attractive. Disease-specific considerations also influence donor choice. Benign hematological disorders require complete HLA matching to minimize complications, while in malignant diseases, partial HLA mismatches might be accepted to enhance graft-versus-tumor effects. Hodgkin lymphoma patients demonstrate superior outcomes with haploidentical donors compared to MUDs, challenging conventional hierarchies. Donor exclusion criteria encompass medical conditions that may increase donation-related risks or compromise graft quality. These include cardiovascular, pulmonary, hematological, and immunological disorders, active infections, and malignancy history. As transplantation practices evolve, personalized donor selection algorithms incorporating disease characteristics, patient factors, donor availability, and center experience are replacing rigid hierarchies, ultimately improving outcomes for patients requiring allogeneic HSCT.

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Abstract 044

GENE THERAPY IN HEMOPHILIA

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Symptomatic or prophylactic treatment of hemophilia began in the 1960s with fresh frozen plasma therapy. Over the years, treatment evolved through plasma-derived products, recombinant therapies, extended half-life products, and

subcutaneous treatments. However, achieving zero bleeding has remained elusive. In 2022, gene therapies received regulatory approval, offering hope for a definitive cure for hemophilia. Ege University joined gene therapy clinical trials in 2021. Our patient, MA, born in 1998 and diagnosed in 2000, had a childhood marked by frequent bleeding and target joint involvement despite starting prophylaxis. During gene therapy screening, he was found to be AAV5 seronegative and was invited to our clinic. Following gene therapy, it was as if he was reborn. His initial Factor VIII level of 0.1 IU/dL rose to 128 IU/dL by week 208. His HJHS score dropped from 15 to 8, and he experienced no bleeding episodes. Türkiye Hemophilia is an ideal candidate for gene therapy because it is a single-gene disorder with a simple expression loss, even low levels of expression are clinically effective, no specific tissue or cell targeting is required and the factor is secreted directly into plasma and can be easily measured. Initial preclinical studies (early 2000s) using both viral and non-viral methods showed limited efficacy but no significant side effects. Adequate FVIII expression was not achieved. AAV-based somatic gene therapy for hemophilia was approved and commercialized in 2022–2023. AAV is ideal for gene transfer due to its non-pathogenic nature, defective self-replication, long-term

transgene expression, availability of different serotypes for different tissues. The goal of gene therapy is to insert normal FVIII/FIX genes into the liver, enabling liver cells to synthesize these clotting factors. In the HOPE-B study, mean FIX activity was 39.0 IU/dL at 6 months (± 18.7 ; range 8.2–97.1), 36.7 IU/dL at 24 months (± 19.0 ; range 4.7–99.2). In the GENE2 study, 75.4% of patients had FVIII activity >5 IU/dL at year 2. However, factor expression varied significantly among patients. Challenges in Hemophilia Gene Therapy are high sero-prevalence of AAV antibodies, potential reduction in factor synthesis due to antibody development and risk of liver damage. The limitations of gene therapy are variable treatment response between patients, durability and applicability of the therapy, many patients already have AAV antibodies, higher vector genome doses may be required, increasing toxicity risk, immune reactions against the capsid may lead to loss of transfected hepatocytes, uncertainty in children, inhibitor-positive patients, and those with liver disease, re-dosing is not possible due to antibody development and high cost. To overcome these limitations, new gene technologies are being explored.

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