American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Introduction to the How I Treat Series on "How I Manage High-Risk Patients Following Allogeneic Transplant"

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Robert Zeiser (University Medical Center Freiburg, Germany)

Abstract:

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Introduction to the How I Treat Series on “How I Manage High-Risk Patients Following Allogeneic Hematopoietic Cell Transplantation.”

Robert Zeiser[1]
[1] Associate Editor, Blood

To improve the therapeutic success of allogeneic hematopoietic cell transplantation (allo-HCT) the management of high-risk patients is essential. High-risk means high likelihood for development of graft-versus-host disease, for relapse of the underlying malignancy and for severe infectious complications. The following "How I treat" series describes the state-of-the art and the major recent developments in the management of prevention of relapse with cellular therapies or maintenance-based approaches, GVHD prophylaxis and prevention of viral reactivation:

Alexander Biederstädt, Katayoun Rezvani, “Use of pre-emptive T cell/ NK cell transfer in patients with high-risk leukemia”
Zachariah DeFilipp, Yi-Bin Chen, “How I Treat with Maintenance Therapy after Allogeneic HCT”
Joseph Rimando, Shannon McCurdy, Leo Luznik, “How We Prevent GVHD in High Risk Patients: Post Transplant Cyclophosphamide and Beyond”
Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh, “Prevention of viral reactivation in high-risk patients”

Relapse of high-risk leukemia after allo-HCT remains a major clinical challenge. The article on the use of pre-emptive T cell/NK cell transfer highlights cellular therapies that can be used to prevent or treat relapse. Response rates of relapsed acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) to donor lymphocytes (DLI) are low and the role of pre-emptive DLI upon detection of measurable residual disease (MRD) is unclear due to the lack of prospective randomized studies. Biederstädt and Rezvani discuss the challenges of MRD-triggered DLI treatment after allo-HCT, they outline novel approaches of post-allo-HCT cellular therapies, including the role of Chimeric Antigen Receptor (CAR)-redirected cellular therapy and T cell receptor (TCR) gene therapy. Additionally, a practical structure for the decision-making process whether to use preemptive cellular therapy or not for patients with high-risk leukemia is provided.

Besides cellular therapy-based approaches, drug-based maintenance therapy after allo-HCT has shown encouraging results in certain types of high-risk leukemias, which is the topic of the article by DeFilipp and Chen. The authors discuss risk factors that impact the decision to initiate maintenance therapy after allo-HCT including the biology of the leukemia, the patients MRD status before and after allo-HCT and the intensity of the conditioning regimen. This information may guide the decision on the use of maintenance therapy for the more selective treatment of patients at high risk of relapse while sparing other patients. The article connects common case scenarios with the currently available therapeutic agents including FLT3 inhibitors, isocitrate dehydrogenase (IDH) 1 and 2 inhibitors, BCL-2 inhibitors, BCR-ABL1 tyrosine kinase inhibitors and hypomethylating agents in the context of published data and ongoing studies.

Severe acute GVHD and related infectious complications are still major causes of death in high-risk patients. Luznik and colleges debate the emergence of new GVHD risk factors including novel immunotherapies prior and after allo-HCT, the need for early cessation of immunosuppression, use of maintenance therapies in the post allo-HCT setting and older recipient age. They provide strategies to cope with such high-risk for GVHD constellations using post-transplantation cyclophosphamide (PTCy) and other GVHD prophylaxis approaches. The success of PTCy as well as the side effects of this strategy are discussed. The authors use

illustrative cases to connect PTCy based approaches for GVHD prophylaxis and discuss combination approaches with abatacept and JAK inhibitors.
Reactivation of viruses is one of the most common and life-threatening infectious complications after allo-HCT. Boeckh and colleges discuss the role of pharmacological or immune intervention-based prevention for herpes simplex virus, varicella zoster virus, and cytomegalovirus for high risk patients undergoing allo-HCT in light of recent clinical trials. Using illustrative clinical cases they also debate the fewer approaches available for effective prevention of for HHV-6, EBV, Adenovirus and BK virus infections. Ongoing clinical trials testing virus-specific cellular therapies, both single and multi-target, as well as new vaccines are presented. To guide clinical decision making, the authors provide risk-adapted recommendations for prevention and treatment of viral reactivation based on clinical practice at three US Medical Centers with high allo-HCT activity.

This "How I treat" series highlights insights into novel therapeutic strategies for patients at high-risk for relapse, GVHD and viral reactivation after allo-HCT. A major goal of this series is to provide the treating physician with an overview of novel therapeutic targets that are either already approved or in clinical testing to offer optimal clinical care for high-risk patients undergoing allo-HCT.