POST-REMISSION CONSOLIDATION AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: FACT OR FICTION

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Allogeneic hematopoietic-cell transplantation (HCT) is typically reserved for malignant hematologic diseases that are associated with high-risks for relapse following conventional chemotherapy. In these high-risk patients, the expectation is that the conditioning regimen chemotherapy and/or radiation therapy along with the alloreactive graft-versus-tumor (GVT) effect will lead to long-term remissions and a potential cure. However, up to half of all allogeneic HCT recipients do not benefit from this aggressive treatment approach and can relapse after HCT. Although advances in transplantation technology and supportive care practices have led to continuing improvements in survival over time, these improvements have largely been the result of reduced risks of early and late treatment related mortality (TRM) (1,2). Risks of relapse have not changed substantially and relapse continues to be the main cause of death early post-transplantation and among the important causes of death among long-term survivors (1-3). Maintenance therapy after transplantation is an attractive strategy that is under consideration to reduce the risks of relapse among allogeneic HCT recipients. This paper reviews the general risk factors for relapse, monitoring for relapse and the rationale and prevalent understanding of maintenance therapy after allogeneic HCT.

Risk factors for relapse

Patients with unacceptably high risks of relapse are obvious candidates for post-transplantation maintenance therapy. Such patients have to be ideally identified prior to transplantation or early post-transplantation. Disease and disease stage are the strongest predictors for relapse. The GVT response has been observed to be most potent in patients with chronic myeloid leukemia (CML), moderately effective among patients with low grade lymphoid malignancies, and although present, is not as robust in patients with other diseases. Additionally, this effect is also dependent upon disease stage and disease bulk at transplantation. Patients with early stage disease (e.g. CML chronic phase versus accelerated or blast phase) and minimal disease (e.g. acute myeloid leukemia [AML] in complete remission instead of relapsed or refractory disease) have a lower probability of relapse. Disease-specific prognostic factors, which often are the basis for considering transplantation as a therapeutic option in the first place, are also associated with an increased risk of relapse after HCT (e.g., Philadelphia chromosome positive acute lymphoblastic leukemia [ALL] or AML and myelodysplastic syndromes [MDS] with poor-risk cytogenetic abnormalities). Transplant related factors such as graft source, graft manipulation (e.g., T-cell depletion) and conditioning regimen intensity can also affect the risk of relapse after transplantation.

Monitoring for relapse after allogeneic transplantation

Another consideration for maintenance therapy is ability to detect minimal residual disease (MRD). Patients with high burden of MRD pre-transplantation can be candidates for maintenance therapy and

monitoring for MRD would have important implications for initiating or discontinuing maintenance therapy post-transplantation. One of the major challenges to monitoring for MRD is the lack of standardized approaches. Depending on the underlying disease, methods for disease monitoring can be less sensitive techniques such as chromosome banding or fluorescent in-situ hybridization (FISH) analysis or highly sensitive techniques such as multiparameter flow cytometry and molecular methods for disease detection (e.g., polymerase chain reaction [PCR]) (4).

Maintenance therapy after allogeneic HCT

Although the rationale of using drug therapy to maintain a minimal residual disease status in order to give an advantage to the GVT effect is attractive, data supporting this approach are lacking and it needs to be explored in prospective clinical trials. Examples of drugs that warrant investigation as prophylactic therapy include targeted agents such as tyrosine kinase inhibitors (e.g. imatinib, dasatinib and nilotinib) for CML and Philadelphia chromosome positive ALL and FLT-3 inhibitors (e.g. lestaurtinib) for FLT3 internal tandem duplication mutation positive AML and non-targeted agents such as immunomodulatory drugs (e.g. lenalidomide) and bortezomib for high-risk multiple myeloma and hypomethylating agents (e.g., decitabine and azacytidine) and histone deacetylase inhibitors (e.g., vorinostat) for AML and MDS (Table 1). Monoclonal antibodies such as rituximab are attractive candidates for maintenance therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Several clinical trials are evaluating the role of a variety of pharmacologic maintenance therapy approaches. Many agents have immunomodulatory properties and can impact the risks of graft-versus-host disease (GVHD). For example, a recent trial reported from the HOVON group showed a high incidence of acute GVHD among patients receiving lenalidomide maintenance after non-myeloablative HCT for multiple myeloma (5). Cellular therapies such as the use of donor lymphocyte infusions or administration of natural killer cells after allogeneic HCT are examples of non-pharmacologic approaches under investigation to prevent relapse.

Maintenance therapy after allogeneic HCT: Future research

Current understanding of the role of maintenance therapy among allogeneic HCT recipients is very limited. Efficacy of such therapy has to be balanced with its costs and toxicity. Clinical trials are ongoing and more trials are needed to better address a number of unanswered issues (Table 2). First, robust disease specific models are needed to better identify patients who are at high-risk for relapse post-transplant and would benefit the most from maintenance therapy. Secondly, the best time to initiate maintenance therapy and its duration needs to be better defined. Better and standardized methods to detect and monitor MRD are important components of preventive therapy using pharmacologic agents. The toxicity of these agents, including myelosuppression and impact on risks and severity of GVHD also needs to be evaluated. Many allogeneic HCT recipients receive prolonged therapy to prevent or treat infections and GVHD and drug-drug interactions with agents used for maintenance therapy will need to be studied. Finally, the majority of agents being explored for maintenance therapies are expensive and costs and cost-effectiveness of these drugs will need to be investigated.

Table 1. Representative examples of agents that can be considered for further investigation as maintenance therapy after allogeneic transplantation

Disease	*Agent*
Non-targeted agents	
AML	Decitabine, 5-azacytidine, vorinostat
MDS	Decitabine, 5-azacytidine, lenalidomide
Mutliple myeloma	Thalidomide, lenalidomide, bortezomib
NHL	Bortezomib
Targeted agents	
ALL (Ph+)	Imatinib, dasatinib, nilotinib
AML (FLT3+)	Lestaurtinib
CLL	Rituximab, alemtuzumab
CML	Imatinib, dasatinib, nilotinib
Myelofibrosis	JAK2 inhibitors
NHL	Rituximab, alemtuzumab

ALL, acute lymphoblastic leukemia; **AML,** acute myeloid leumkeima; **CLL,** chronic lymphocytic leukemia; **CML,** chronic myeloid leukemia; **CML,** chronic myeloid leukemia; **MDS,** myelodysplastic syndrome; **NHL,** non-Hodgkin's lymphoma

Table 2. Issues to consider and areas for future research regarding maintenance therapy following allogeneic hematopoietic cell transplantation.

Models to identify pre-transplantation or early post-transplantation patients at high risk for relapse
Standardized methods for evaluating and measuring minimal residual disease
Duration of maintenance therapy
Costs and cost-effectiveness of maintenance therapy
Short-term and long-term toxicity associated with maintenance therapy
Drug-drug interactions and impact of maintenance therapy on immue-recovery and graft-versus-tumor effect

References

1. Horan JT, Logan BR, Agovi-Johnson MA, et al. Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? J Clin Oncol. 2011;29:805-813.
2. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2011;29:2230-2239.
3. Bishop MR, Alyea EP, 3rd, Cairo MS, et al. National Cancer Institute's First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: summary and recommendations from the organizing committee. Biol Blood Marrow Transplant. 2011;17:443-454.
4. Kroger N, Bacher U, Bader P, et al. NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: report from the Committee on Disease-Specific Methods and Strategies for Monitoring Relapse following Allogeneic Stem Cell Transplantation. Part I: Methods, acute leukemias, and myelodysplastic syndromes. Biol Blood Marrow Transplant. 2010;16:1187-1211.
5. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. Blood. 2011;118:2413-2419.
6. Olavarria E, Ottmann OG, Deininger M, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia. 2003;17:1707-1712.
7. Mielcarek M, Storer BE, Flowers ME, Storb R, Sandmaier BM, Martin PJ. Outcomes among patients with recurrent high-risk hematologic malignancies after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2007;13:1160-1168.
8. Miller JS, Weisdorf DJ, Burns LJ, et al. Lymphodepletion followed by donor lymphocyte infusion (DLI) causes significantly more acute graft-versus-host disease than DLI alone. Blood. 2007;110:2761-2763.