Biol Blood Marrow Transplant 22 (2016) 2134–2140

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Strategies and Challenges for Pharmacological Maintenance Therapies after Allogeneic Hematopoietic Cell Transplantation

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Article history:
Received 1 August 2016
Accepted 12 August 2016

Key Words:
Maintenance
Allogeneic
Transplantation
Pre-emptive

A B S T R A C T

Disease relapse is a major barrier to successful allogeneic hematopoietic cell transplantation (HCT). Maintenance therapy administered after HCT is a promising strategy to attempt to reduce relapse and improve overall survival. However, many questions and challenges remain regarding this approach, including which patients should receive maintenance therapy, which agents should be used, what the ideal duration of therapy is, and what effect specific agents will have on toxicities, immunological reconstitution and graft-versus-host disease. Clinical trials are ongoing, which should help begin to address some of these issues and it is imperative that the transplantation community continues to collaborate in such trials to best answer these questions.

INTRODUCTION

Disease relapse represents the leading cause of failure after allogeneic hematopoietic cell transplantation (HCT) [1,2]. Although progress has been made to reduce transplantation-related mortality through better patient selection, improved supportive care, and higher resolution HLA typing, the risk of relapse has not decreased significantly over the last 2 decades [3,4]. Furthermore, the risk of relapse has become an increasing concern for biologically high-risk patients, who have been identified through better risk stratification and who are increasingly able to undergo HCT because of improvements in disease control through combination chemotherapy regimens as well as targeted inhibitors and immunotherapies [5]. *Maintenance therapy*, defined as therapy initiated while the patient remains in complete remission (CR), is a promising approach to reduce the rate of relapse after allogeneic HCT [6]. However, this approach is not without challenges, as there is a balance in attempting to provide additional anticancer activity while not causing additional immunosuppression, inducing graft-versus-host disease (GVHD) or accruing toxicities. Here, we review the current state of maintenance therapies after allogeneic HCT and address challenges and future directions in this field.

RATIONALE FOR MAINTENANCE STRATEGIES AFTER ALLOGENEIC HCT

A number of approaches to therapy after allogeneic HCT exist, which can most broadly be characterized as maintenance therapy, pre-emptive therapy, or therapy for active relapsed disease (Figure 1). Therapy for relapsed disease after allogeneic HCT has been comprehensively reviewed elsewhere [4,5] and will not be discussed here. The distinction between maintenance and pre-emptive therapy lies in the detection of minimal residual disease (MRD). Maintenance therapy refers to therapy that is started after HCT while the patient remains without detectable disease, whereas pre-emptive therapy is triggered by the detection of MRD. The maintenance and pre-emptive approaches each have their own advantages and disadvantages. The pre-emptive approach allows for a more individualized strategy, only beginning therapy in those who show early signs of disease progression via detectable MRD, while sparing further therapy for those who remain with undetectable disease. This approach is much akin to the current management of cytomegalovirus reactivation after HCT [7]. However, the pre-emptive approach requires sensitive and clinically reliable assays to detect MRD in the post-HCT setting. It also is only effective if the kinetics of relapse allow sufficient time from MRD detection to initiate therapy before morphologic relapse. In contrast, the maintenance approach involves treating all patients, and thus, inherently overtreating a significant number of patients who otherwise would not have needed such therapy. Therefore, maintenance therapy requires an agent that does not cause much added toxicity or other effects; namely, inducing GVHD. Ultimately, the decision to use a

Financial disclosure: See Acknowledgments on page 2139.

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http://dx.doi.org/10.1016/j.bbmt.2016.08.021
1083-8791/

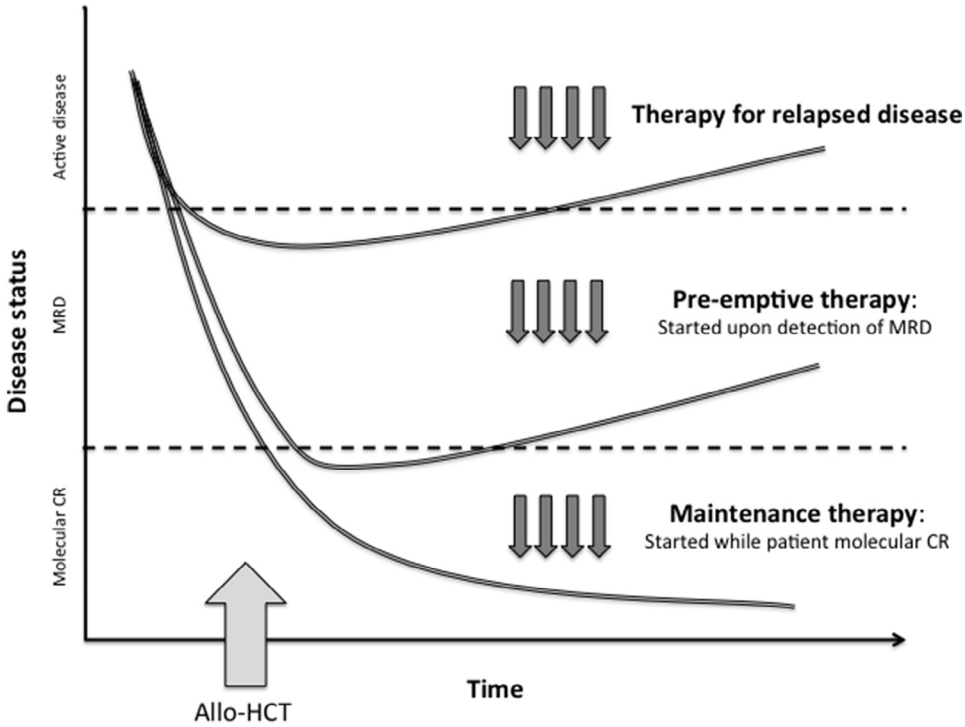

Figure 1. Approaches to post-transplantation therapies after allogeneic HCT.

maintenance therapy for an individual patient depends on the risk of disease relapse balanced by the potential benefit and toxicity of the agent in question (Table 1). Only through well-designed clinical trials will we be able to make such informed decisions.

DISEASE-SPECIFIC APPLICATIONS OF MAINTENANCE THERAPY

A number of studies that have directly explored the use of maintenance therapy after allogeneic HCT have been published or presented (Table 2), although the issue has been addressed indirectly in several other reports. This review focuses on pharmacological agents and does not include interventions involving donor leukocyte infusion or other cellular therapies. Herein, we discuss published or presented data, ongoing trials, and future directions of maintenance therapy in a disease-specific manner.

Table 1
Factors Affecting Decisions Regarding Maintenance Therapy after Allogeneic HCT

Factors
Disease-related factors
Underlying disease
Disease response to treatment before transplantation
Transplantation related factors
Intensity of conditioning
Disease status at transplantation
MRD at transplantation
Development of severe acute GVHD
Maintenance therapy related factors
Mechanism of action
Pretransplantation response to maintenance agent, if applicable
Anticipated toxicities
Need for dose reduction
Does not induce or worsen GVHD
Drug interactions with immunosuppression
Duration of therapy

Acute Myeloid Leukemia/Myelodysplastic Syndrome

The most popular approach to post-HCT maintenance therapy for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) is the use of DNA hypomethylating agents (HMA), which have already demonstrated efficacy in the pre-HCT setting [28,29]. HMA are thought to silence tumor-suppressing genes through epigenetic modification and may also enhance the graft-versus-leukemia effect (GVL) through increased expression of tumor antigens. After an initial promising report of the use of azacitidine as maintenance after HCT [30], a phase I study enrolling 45 patients established an optimal dosing schedule for azacitidine to be 32 mg/m^2 s.c. $\times$ 4 cycles and resulted in 1-year event-free survival and overall survival (OS) of 58% and 77%, respectively [8]. Reversible thrombocytopenia was the dose-limiting toxicity. Interestingly, no change in global DNA methylation was detected, suggesting that the potential therapeutic effect may not actually be related to DNA hypomethylation. A phase I study of 27 patients with AML further supported the tolerability of azacitidine after HCT and found that azacitidine both augmented expansion of regulatory T cells and induced cytotoxic CD8$^+$ T cell response to several tumor antigens, which in part could explain a favorable balance between GVHD and GVL [9]. A phase II National Cancer Institute/Alliance trial (CALGB 100801) enrolled 66 patients, but only 42 were able to initiate treatment with azacitidine and just 17 completed all 6 cycles as planned, questioning the overall feasibility of such agents as maintenance [31]. In the only study to date to investigate a dual-agent maintenance strategy, azacitidine and gemtuzumab ozogamicin (anti-CD33 antibody-drug conjugate) were administered every 4 weeks for up to 4 cycles [10]. The combination resulted in