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PROGRESS IN HEMATOLOGY

Prophylactic or pre-emptive therapies to prevent relapse after allogeneic stem cell transplantation

Prophylactic or pre-emptive therapies to prevent relapse after allogeneic hematopoietic stem cell transplantation

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Abstract

Allogeneic hematopoietic stem cell transplantation is a potent curative treatment for hematological malignancies, but relapse is still a major problem. Donor lymphocyte infusion (DLI) and maintenance therapies after transplantation are promising strategies to reduce the risk of relapse. DLI augments the graft-versus-tumor effect by directly adding allo-reactive donor lymphocytes, and has been used in relapsed patients. In this Progress in Hematology (PIH), we will focus on prophylactic or pre-emptive DLI, including DLI from a haploidentical donor. On the other hand, specific drugs, which are used in maintenance therapies for each disease, kill tumor cells directly and/or immunologically by stimulating immune cells. Maintenance therapies should be started early after transplantation without severe myelosuppression. Molecularly targeted drugs are therefore suitable for use in maintenance therapies, and are reviewed in this PIH. The optimal application of these strategies has not yet been established. However, important evidence regarding their efficacies, adverse events, and effects on immune systems is accumulating, and could help to improve outcomes in allogeneic transplantation.

Manuscript

Allogeneic hematopoietic stem cell transplantation is a potent curative treatment for hematological malignancy. The combination of pre-transplant conditioning and a graft-versus-tumor (GVT) effect after transplantation by donor cells has the potential to eradicate the disease [1–3]. However, relapse is still a major problem after transplantation [4–6]. To reduce the risk of relapse, several treatment strategies after transplantation have been considered. Of these, we focus on two kinds of additional therapies after transplantation, donor lymphocyte infusion (DLI) and maintenance therapies, in this Progress in Hematology (PIH). These strategies are especially important in patients with high-risk disease in whom the relapse rate is high even with a high-intensity pre-transplant conditioning regimen and in patients who undergo transplantation with reduced-intensity conditioning in which a low non-relapse mortality is often counterbalanced by a high relapse rate [7, 8].

DLI is a treatment strategy that augments the GVT effect by directly adding allo-reactive donor lymphocytes. The efficacy of DLI was first demonstrated in patients with chronic myelogenous leukemia (CML) who had relapsed as CML-chronic phase [9]. However, DLI has only a limited effect on hematological relapse of acute leukemia or myelodysplastic syndrome (MDS) [10–12]. Therefore, the timing is key for the success of DLI in this situation. Another key point is the number of infused donor lymphocytes, which should be determined based on the donor type and the disease risk [13]. In this PIH, Dr. Kaito Harada reviewed the outcomes of prophylactic DLI or pre-emptive DLI [DLI that is performed for patients with mixed chimerism or those with minimal/measurable residual disease (MRD)], including DLI from a haploidentical donor.

The aim of maintenance therapies after transplantation is to kill tumor cells directly and/or immunologically by stimulating immune cells. Maintenance therapies after transplantation are administered before hematological relapse, and therefore, these therapies should be started early after transplantation. Considering the optimal timing of administration, cytotoxic drugs are difficult to use, because the risk

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of severe myelosuppression and organ damage will be high. Recently, many kinds of molecular target drugs have been used for various hematological malignancies. These drugs often have different profiles regarding adverse effects compared to the conventional cytotoxic drugs [14]. Generally, molecular target drugs are less myelosuppressive than cytotoxic drugs, and therefore, are more suitable for maintenance therapies early after transplantation. On the other hand, caution should be paid to their interaction with the other drugs and the immunological effects of these new drugs [15]. In this PIH, we focus on maintenance therapies after transplantation for acute myeloid leukemia (AML)/MDS, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL), and multiple myeloma (MM).

Azacitidine has been shown to be effective in patients with MDS, and recently also in patients with AML [16, 17]. FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) is observed in about 25% of patients with AML [18]. AML patients with FLT3-ITD are classified as having intermediate-risk disease in the 2022 European Leukemia Net (ELN) risk classification, and allogeneic transplantation in the first complete remission (CR1) is recommended in such patients [19]. The efficacies of several kinds of FLT3 inhibitors have been evaluated and used in practice before and after transplantation [20, 21]. Dr. Yuho Najima reviewed the prophylactic or pre-emptive use of azacitidine or FLT3 inhibitors after transplantation in patients with AML or MDS.

Treatment outcomes of patients with Ph + All have dramatically improved since the advent of tyrosine kinase inhibitor (TKI). Many studies have supported the inclusion of TKI into the first-line treatment [22–24], and this evidence is still being updated with the second [25–27] and third generations of TKIs [28, 29]. Dr. Hideki Nakasone reviewed the prophylactic or pre-emptive use of TKI after transplantation in patients with Ph + ALL.

The combination of novel efficient drugs and autologous transplantation has improved the prognosis of patients with MM [30, 31]. On the other hand, evidence regarding allogeneic transplantation for MM is limited [32, 33], especially after the advent of novel drugs, such as proteasome inhibitors (PIs) [34], immunomodulatory drugs (IMiDs) [35], and monoclonal antibodies [36]. Therefore, evidence regarding maintenance therapy after allogeneic transplantation in patients with MM is much more limited, unlike the reliable evidence that is available after autologous transplantation [37]. However, allogeneic transplantation is still the only curative treatment, and maintenance therapy after transplantation seems to play a role. Dr. Koji Kawamura reviewed the prophylactic or pre-emptive use of IMiDs and/or PIs after transplantation in patients with MM.

The optimal application of DLI and maintenance therapies after allogeneic transplantation has not yet been established. However, there is a growing body of evidence regarding their efficacies, adverse events, and effects on immune systems. We hope that DLI and maintenance therapies will continue to improve the outcomes of allogeneic transplantation and this PIH may further this goal.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest S.K. has received honoraria from Chugai Pharmaceutical Co., Ltd.

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