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REVIEW

Donor lymphocyte infusions for relapse after allogeneic transplantation. When, if and for whom?

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ABSTRACT

Donor lymphocyte infusion (DLI) using unstimulated leukapheresis is one of the most effective treatment strategies for patients with hematological malignancies; its graft-versus-leukemia effects make it especially effective in chronic myeloid leukemia patients who relapsed after allogeneic stem cell transplantation (allo-HSCT). However, DLI application is limited by the development of graft-versus-host disease and aplasia, and thus cannot be routinely applied for prophylaxis. Therefore, important questions remain to be answered, such as when, and whom to DLI? Recent advances enable DLI using allografts of granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells; allodepleted donor T cells; and infusions of donor-derived, ex vivo-expanded, $CD8^+$ cytotoxic T lymphocyte, which can decrease relapse and improve transplant outcomes. Preemptive immunotherapy of relapse was also introduced based on the determination of mixed chimerism and minimal residual disease. In this review, we summarize the latest developments in recent strategies that will affect future DLI efficacy — focusing on the disadvantages and advantages of each protocol for the treatment, preemptive therapy, and prophylaxis of relapse.

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important curative therapy for hematological malignancies.[1–3] However, the relapse rate is still a problem for patients undergoing allo-HSCT, especially those with advanced-stage disease.[4–7] Its graft-versus-leukemia (GVL) effects make donor lymphocyte infusion (DLI) currently one of the most effective strategies for patients with recurrent hematological malignancies after allo-HSCT.[5,8–35] In 1990, Kolb et al.[36] provided the first evidence suggesting a potent GVL effect after DLI for patients with chronic myeloid leukemia (CML) relapse; this was later confirmed by several researchers who showed complete remission (CR) in 70–80% of patients with chronic CML relapse. Unfortunately, application of DLI is limited by the development of graft-versus-host disease (GVHD) (40%–60%) and aplasia (20%–40%), thus DLI cannot be routinely used for prophylaxis of relapse after allo-HSCT.[8,32,37,38] These limitations have prompted researchers to investigate other strategies to decrease relapse after transplantation, such as infusion of granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood progenitor cells,[5,9,16] modified DLI,[10–12,15,16] and infusion of allodepleted donor T cells.[14,39] The present review summarizes the recent advances that have been made using the above-mentioned strategies in improving treatment and prophylaxis of relapse after human leukocyte antigen (HLA)-identical transplantation or unmanipulated haploidentical blood and marrow transplantation (HBMT).[14,39] We also discuss the disadvantages and advantages of each protocol that will affect future DLI efficacy.

2. Therapeutic DLI

DLI is a powerful weapon in the treatment of relapsed or persistent hematological malignancies following allo-HSCT.[8,12,36,40–42] Recent advances in DLI have focused on enhancing the GVL or graft-versus-tumor effects of the infused donor T cells, while decreasing DLI-related toxicities, such as GVHD and aplasia.[14,15,39,43,44]

2.1. Modified DLI for relapse treatment after HSCT

The roles of traditional DLI and escalating-dose DLI in patients with recurrent hematological malignancies after allo-HSCT have been recently reviewed elsewhere.[8,45,46] Here we focus mainly on the infusion of G-CSF-mobilized peripheral blood progenitor cell.[9,41,45] Previous study showed multiple biological effects of G-CSF on peripheral blood stem cells, such as the ability to polarize T cell from Th1 to Th2 and the promotion of regulatory T cell and tolerogenic dendritic cell differentiation.[47,48] Huang et al.[40] reported that G-CSF-mobilized peripheral blood progenitor cell infusion produces superior disease-free survival

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(DFS) in patients who received unprimed lymphocytes for relapse after allo-HSCT, although the difference in the incidence of severe GVHD was not significant. Choi et al.[41] described sixteen patients who received chemotherapy followed by G-CSF-mobilized peripheral blood progenitor cell infusion with a median $CD3^+$ cell dose of 4.5 (range, 1.6–8.3)$\times 10^8$/kg. The authors reported 10 of 16 patients achieving CR, with four patients maintaining remission for over two years. OS at 2 years was estimated at 31%. Of 13 assessable patients, 12 developed acute GVHD at a median of 23 days after DLI (range, 6–41 days): one with grade I, three with grade II, five with grade III, and three with grade IV. This result may be related to the fact that no post-DLI GVHD prophylaxis was administered in this patient cohort. Hasskarl et al.[9] demonstrated that G-CSF-stimulated DLI derived from allogeneic grafts is safe and immunoreactive, and can be applied early in cases of mixed chimerism and molecular or cytogenetic relapse. Taken together, our data[10–13,15,16] and those from other groups[9,41,49] suggest that CSF-mobilized cell infusion may be substituted for conventional infusion of donor lymphocytes.

To further decrease the incidence of GVHD, short-term immunosuppressive (STI) agents have been introduced, including cyclosporine A or methotrexate. A recent study evaluated 54 patients who received STI agents for prophylaxis against DLI-associated GVHD.[13] Seventeen patients experienced acute GVHD, 30 patients developed chronic GVHD, and no GVHD-related death was observed. A significant difference in the incidence of DLI-associated acute GVHD was observed between the group that received no prophylaxis against GVHD or received prophylaxis for less than two weeks and the group that received prophylaxis for over two weeks ($P=0.000$); no difference was observed in the relapse rate for prophylactic DLI patients between the two groups. These results suggest that STI agents may reduce DLI-associated acute GVHD without influencing graft-versus-leukemia (GVL) effects and survival after G-CSF-mobilized peripheral blood progenitor cell infusion.[16] As an alternative to infusion of G-CSF-mobilized peripheral blood progenitor cell without GVHD prophylaxis, a modified DLI protocol was established, which entails the infusion of G-CSF-mobilized peripheral blood progenitor cell followed by the use of STI for GVHD prophylaxis.[5,10–13] This strategy is associated with less GVHD, and post-DLI immune suppression does not reduce the GVL effects.[10–13,15,16] In 20 patients, we investigated the efficacy and safety of modified DLI at a median of 177 days after haploidentical HSCT. Eight patients survived in CR for a median of 1118 days. The 2-year probability of LFS was 40%. Acute GVHD grade II–IV occurred in six patients after DLI, and GVHD prophylaxis reduced the incidence of acute GVHD. These primary data show the modified DLI protocol to be a potentially effective therapeutic option for patients who relapse after haploidentical HSCT.[10] The incidence of GVHD after post-HBMT DLI was acceptable, although the median $CD3^+$ T cell dose with G-CSF-mobilized peripheral blood progenitor cell was 0.61 (range, 0.23–4.62)$\times 10^8$/kg, which was higher than those reported by others.[32,50] Our group further showed that, compared to chemotherapy alone, chemotherapy followed by modified DLI achieved a higher CR rate, longer CR duration, lower cumulative risk of relapse, and superior DFS (Yan et al. in preparation). Multivariate analyses confirmed that chronic GVHD after intervention and chemotherapy followed by modified DLI was significantly correlated with a higher CR rate, lower relapse rate, and better DFS, indicating that chemotherapy followed by modified DLI is safe and efficacious and could improve survival in patients with post-transplant relapsed leukemia.

2.2. Infusion of allodepleted donor T cells

Maury et al.[14] performed a phase I/II study including 17 patients who had experienced relapse after transplant and never displayed any clinical response to standard DLIs. Tregs were depleted from DLI without affecting natural killer cells; the cell depletion rates of $CD3^+CD25^+$ and $CD4^+FoxP3^+$ cells were $96\pm 7\%$ and $98\pm 5\%$, respectively. A mean Treg-depleted DLI cell dose of 4.3 (range, 1–10)$\times 10^7$ $CD3^+$ cells/kg was infused, without any acute infusion-related toxicity. Seven of the 17 treated patients are alive, and five of them disease-free, with a mean follow-up of 24 months after their first Treg-depleted DLI for surviving patients. The authors also demonstrated an association between GVHD and improved survival. These results are promising, and suggest that depletion of Treg in allografts may enhance GVL effects. However, more clinical studies are required to confirm the efficacy and safety of this technique before it can be routinely applied.

In a CML patient, Zhang et al.[51] found that $CD4^+$ cell DLI led to a rapid expansion of pre-existing marrow-resident leukemia-specific $CD8^+$ T cells, followed by a cascade of peripheral B and T antigen-specific immune responses. In another study at the University of Hamburg, $CD4^+$-selected DLI was used to treat relapse and infection in 24 patients who underwent transplantation.[39] During a median follow-up of 25 months, seven patients experienced GVHD (acute II–IV: 17%; acute III–IV: 8%; chronic: 12%), 13 of 21 further evaluable patients (62%) showed measurable clinical response, and two patients with therapy-refractory infectious complications (herpes simplex virus) showed remarkable immunologic improvement. The 2-year DFS for all patients was 82%. However, this high rate is not surprising because of the indolent or chronic nature of the disease studied. Therefore, it is currently difficult to recommend $CD4^+$-selected DLI as an alternative option to unprimed DLI due to several key limitations of the study, including the limited and heterogeneous cohort of patients, varied indications to treatment, and presence of additional therapy.[39] Moreover, the incidence of GVHD after $CD4^+$-selected DLI should be further studied, because donor $CD4^+$ T cells are thought to be essential for inducing delayed host tissue injury in chronic GVHD, although memory $CD4^+$ T cells failed to induce GVHD.[52–54]

2.3. Infusion of mHAg-specific CTLs

The adoptive transfer of donor T cells that recognize recipient minor histocompatibility antigens (mHAgs) is another potential strategy for treating relapse after allo-HSCT. Warren et al.[44] treated seven leukemia patients who relapsed after HLA-matched transplant with infusions of donor-derived, ex vivo-expanded $CD8^+$ cytotoxic T lymphocytes (CTL) specific for tissue-restricted recipient mHAgs. Before administering T cells, immunosuppressive drugs were withdrawn or reduced in patients being treated for GVHD. Patients then received cytoreductive chemotherapy, followed by a series of three infusions of mHAg-specific CTLs administered at an escalating target dose ($3.3\times 10^7/m^2 \rightarrow 3.3\times 10^8/m^2 \rightarrow 3.3\times 10^9/m^2$) over 11 days. All patients received at least one infusion with a cell dose greater than 2×10^9, and the highest dose administered to each patient ranged from 2.25×10^9 to 6.6×10^9 cells. Pulmonary toxicity of CTL infusion was seen in three patients, was severe in one patient, and correlated with the level of expression of the mHAg-encoding genes in lung tissue. GVHD was observed in three patients. Five patients achieved complete but transient remissions, with one patient still alive after therapy.[44] These results suggest that infusion of mHAg-specific CTLs is feasible. However, it is a technically complex and cumbersome isolation and expansion process that requires special expertise.[55] In addition, tumor-specific immunity can only be restored to selected malignancies, limiting the general applicability of the approach.

3. Preemptive immunotherapy using DLI

DLI is of limited value when initiated during frank hematologic relapse.[8,10,46] Therefore, preemptive immunotherapy using DLI has been introduced by several groups to decrease relapse rates following allo-HSCT.[52,56] Recently, we observed a strong correlation of leukemia-associated aberrant immune phenotypes (LAIP) and Wilms tumor 1 (WT1) with leukemia relapse, DFS, and survival in patients with acute leukemia (AL) receiving allotransplantation.[4,57] Based on these observations and the modified DLI protocol,[11,12,16] we prospectively studied the

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