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Donor lymphocyte infusion in myeloid disorders

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ABSTRACT

A number of modalities including both pharmaceutical and cell-based treatments have long been tested and developed to prevent and treat relapses after allogeneic stem cell transplantation (allo-HSCT). The ability of donor T cells to recognize antigenic structures on leukemic cell surfaces and destroy them is a well-known fact. Based on this fact, the idea of using donor T cells to contribute to the development of adoptive immunotherapy has emerged. Donor lymphocytes are easy to obtain and donor lymphocyte infusions (DLI) have a simple rational while this treatment modality is an effective example of cellular therapy. The group of chronic myeloid leukemia patients who are more likely to benefit from DLI include: a) patients in the chronic phase of hematologic relapse and b) patients with molecular/cytogenetic relapse. DLI appear to be an appropriate treatment option to be used in combination with conventional chemotherapy or hypomethylating agents in the treatment of post-allo-HSCT relapse for acute myeloid leukemia and myelodysplastic syndrome, if:) the burden of tumor is low b) the relapse is at a molecular level rather than an overt hematologic relapse c) the patient has favorable cytogenetic characteristics d) time interval between transplantation and relapse is relatively longer (> 5 months) e) response could be obtained after salvage therapies. In the event that minimal residual disease (MRD) or increasing mixed chimerism is detected, prompt administration of DLI for prophylactic purposes without waiting for a manifest relapse, was found to be effective in inducing a full donor chimerism and overcoming MRD and eventually preventing a manifest relapse.

1. Introduction

The most important and essential part of the management of hematologic malignancies consists of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and resulting graft versus tumor (GVT) effect. Despite the remarkable success of allo-HSCT, relapses, which are common particularly in high-risk patients, appear to be the most important cause of current post-transplant treatment failure and mortality. A number of modalities including both pharmaceutical and cell-based treatments have long been tested and developed to prevent and treat relapses [1]. However, the use of some of these is not feasible due to high toxicity while some of them, such as a second transplantation etc, are far from being applicable in clinical practice due to patient characteristics including age, concurrent disease or performance state.

Two main mechanisms may be responsible for relapses after allo-HSCT: tumor cells may escape from either the impact of pre-transplant conditioning chemotherapy regimens or post-transplant immune control [2]. Malignant cells are believed to escape from immune-mediated killing by expressing a soluble inhibitor factor to inhibit immunosuppressive cells and creating their own “microenvironment” [3]. Therefore, a number of pathways including dendritic cell dysfunction, checkpoint pathway activation, defective tumor antigen presentation or tumor cells resistant to other cellular mechanisms may prevent the occurrence of expected effective immune responses against cancer cells.

Although efforts are made to reduce the risk for relapses by selecting the right patient, right donor and right disorder for transplantation procedures, as a principle, the idea of enabling transplanted donor immune cells to dominate and function appears to be reasonable for reducing the risk for relapses or managing relapses [3]. Historically researchers have aimed at reducing donor T cells to lower the incidence of graft-versus host disease (GVHD) which constituted a major barrier to allogenic transplantations. However, it soon became obvious that T cell depletion was associated with bacterial, viral, fungal and opportunistic infections and might trigger graft failure or relapses [4]. The ability of donor T cells to recognize antigenic structures on leukemic cell surfaces and destroy them is a well-known fact. Based on this fact, the idea of using donor T cells to contribute to the development of adoptive immunotherapy has emerged. Donor lymphocytes are easy to obtain and donor lymphocyte infusions (DLI) have a simple rational while this treatment modality is an effective example of cellular therapy.

Cell-based therapy is promising due to its ability to overcome treatment resistance of malignant cells and eventually, to inhibit or completely destroy the tumor microenvironment, this ability provides

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an effective tumor control. Surely, an ideal cellular therapy should have a low side effect profile in addition to a high antitumor activity [5]. Combining cellular therapeutics with each other and with other treatment modalities may be beneficial in optimizing the outcome.

2. Pathophysiology

In the 80 s, significantly longer "relapse-free survival" detected in those who developed an acute or chronic GVHD revealed that the success of an allo-HSCT was related not only to high-dose conditioning regimens lowering residual tumor burden but also immunological GVT effects [6]. The fact that rapid tapering off immunosuppression in the post-transplant period leads to a reduced incidence of relapses and the use of T-cell depleted grafts is associated with a higher rate of relapses compared to unmanipulated grafts and this provides further evidence that GVT effects are related to donor-derived effective T-cells [4].

In the historical development process, although different from current practice, an example of the use DLI, i.e. the use of adoptive immunotherapy without prior use of any cytoreductive therapy or radiation therapy was reported for the first time by Kolb et al. [7]. They could obtain hematologic and cytogenetic complete remission in three patients with chronic myeloid leukemia (CML) who developed apparent hematologic relapse following allo- HSCT and were treated with interferon alpha and viable buffy coat obtained from donor bone marrow. Researchers reported that the addition of interferon (IFN) alpha to DLI treatment aimed at promoting cytotoxic effects of transplanted cells.

The unique possibility to induce allo-reactivity initiated by T cells following a full HLA-matched allo-HSCT is the recognition of peptides which are not included in the body's own HLA. As many genes are polymorphic and they are likely to include single nucleotide polymorphisms, many proteins in our body have different amino acid structures, although the differences are limited. Based on this fact, saying that twins have identical HLAs is scientifically impossible due to small amino acid variations, although twins are considered to have almost identical HLAs [8]. Finally, based on analyses performed on peptidomes obtained from HLA molecules, there is a 10% difference between HLAs from different individuals depending on genetic polymorphisms [9]. This polymorphic peptide structure triggering immune responses even among individuals who are known to be full matched is referred to as minor histocompatibility antigens (MiHAs). Due to the above-mentioned genetic differences, even they come from an identical donor, T-cell repertoire may recognize many HLA molecules with different peptide structures expressed by the tissues of the recipient as "foreign HLA". Therefore, if polymorphic peptides are presented by hematopoietic cells of the recipient, the recipient's i.e. patient's hematopoietic system including malignant cells, will be eliminated by the donor T cells. Under normal conditions, in the presence of donor cell-dominated hematopoiesis, the expected and desired GVT effect occurs, when active T cells act against recipient-derived hematopoietic cells –malignant clonal cells- that express pleomorphic antigens. However, in the event that T cells also target and attack non-recipient-derived cells or non-hematopoietic cells containing polymorphic peptides, this results in GVHD which is the most unwanted and bothersome outcome associated with allo-HSCT. If the HLA mismatch between donor and recipient is prominent, the potential allo-reactive donor T cell-repertoire will be more likely to recognize recipient derived tissues as foreign tissues [10]. In addition to the presence of the expression a variety of MiHAs in the main target organs of GVHD, including gut, skin and liver, T-cell allo-activity is apparently triggered by a number of factors including conditioning regimens, various pathogens, higher numbers of recipient-derived antigen presenting cells (APC) which are activated by other signaling pathways. Actually, recipient-derived hematopoiesis (of recipient origin) expressing MiHAs which are targeted by T-cells may continue for a while even after an uncomplicated allo-HSCT. Therefore, there is an obvious negative correlation between the time interval between transplantation and the risk for relapse. Furthermore in case of an excessive prolongation of this time interval, T-cell activation, i.e. allo-activity is less likely as the recipient-derived APC would be replaced by the APC of donor origin. Certainly, one should know that the effects of GVT and GVHD may be more intense in case of a partial HLA matching since T-cells would not require APCs to be activated.

During 2 decades after the publication of the study conducted by Kolb et al. in 1990, DLI was tested in a number of diseases and the highest efficacy was detected in the treatment of CML [3]. The mechanism of action and factors affecting the success of DLI has been investigated for many years. Systemic effects of DLI on both cellular and humoral immunity include increased cell neogenesis and the T-cell receptor (TCR) diversity in the repertoire, induction of B-cell lymphocytosis and the development of tumor-specific antibodies [11]. Based on the results from a number of studies, notably from those on solid malignancies, tumor-infiltrating T cells are critical to tumor control [12]. In CML, the main tumor site is the bone marrow which is a microenvironment that also serves as a major immunologic priming area and storage for memory T cells [13]. Considering the idea of accumulating T-cells which are able to take the disease under control in the bone marrow; it is not surprising to detect a higher number of disease specific T cells in the bone marrow rather than periphery in myeloid malignancies. As other evidence of the contribution of marrow infiltrating immune population to the effect of DLI, one should look at the results of the administration of CD4 (+) DLI to 29 patients with relapsed CML in a study conducted by Bachireddy et al. [13]. Pre- In the tyrosine kinase inhibitor (TKI) era, the comparisons between responders and non-responders among patients who received DLI revealed higher levels of CD8(+) T lymphocyte infiltration (< 4%) of the bone marrow in responders. Based on the analysis performed by Bachireddy and Wu, we know that disease burden is lower in the bone marrow of responders and more interestingly no differences were detected regarding CD4(+) cells while the numbers of CD3(+) and CD8(+) cells were both higher in the bone marrow and significantly higher that the periphery [11,13]. In patients unresponsive to DLI, one should question donor cell selection, DLI cell doses, timing of the DLI and –probably most of all– whether the disease itself is suitable for DLI.

3. DLI indications

3.1. Chronic myeloid leukemia

Before the groundbreaking introduction of tyrosine kinase inhibitors, patients with CML were treated with IFN alpha and/or allo-HSCT and in case of the relapse of the disease after allo-HSCT, patients had to receive IFN alpha again or they might undergo a second transplantation, if possible. After the successful interventions of Kolb et al., DLI was also introduced into clinical practice as an important option for the treatment of the cases of CML that have recurred after an allo-HSCT.

In a study published by the European Group for Blood and Marrow Transplantation (EBMT) Chronic Leukemia Working Party in 1995; DLI provided a complete remission in 73% and GVHD occurred in 68% of 135 patients with myeloid malignancies (CML n = 84) relapsed after allo-HSCT(14). Interestingly, DLI did not provide a long-term remission in patients with CML in blastic transformation who achieved remission with chemotherapy while DLI provided a 3-year remission in 87% of patients with relapsed CML in the chronic phase. Investigators reported that GVT effects could occur within 4 weeks after the onset of the treatment, while a cytogenetic and molecular response could be achieved over a period of months. Myelosuppression which is a major complication of DLI was defined by the authors as a manifestation of transfusion associated-GVHD, in other words, a direct toxicity of transplanted lymphocytes to host's hematopoietic cells. Finally, they reported that DLI provided a 2-year survival rate of 67%, in patients with CML relapsed after allo-HSCT.

In another study published by Texas Oncology in 1997, a