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Editorial

New Allogeneic hematopoietic Stem Cell Transplantation Method for Treatment of Malignant Tumor: Hematopoietic Stem Cells + Thymus Transplantation

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EDITORIAL

Allo-HSCT for malignant tumors

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective method for treatment of malignant tumors, including leukemia and cancer [1,2]. The underlying theory is that the allogenic T cells attack the tumor cells. However, allo-T cells also induce graft *versus* host disease (GVHD), which is harmful to the host and often leads to death [3]. Conversely, if the all oreactivity is low, the graft *versus* tumor (GVT) effect may be insufficient and the tumor may relapse. Therefore, a number of methods have been developed to separate GVHD and GVT effects, such as reduced intensity conditioning (RIC), stimulation of donor T cells with tumor antigens *ex vivo*, cytokine blockade (e.g., IL-21, IL-23), depletion of antigen presenting cells (e.g., dendritic cells) and priming lymphocytes (e.g., cells expressing CD62L, CD103, CCR5, or CCR7), modulation of immunosuppressive cells (e.g., regulatory T (Treg) cells, mesenchymal stem cells [MSC]) and effector cells (natural killer [NK] cells or donor lymphocytes), pharmacological agents (e.g. bortezomib, rapamycin, or suberoylanilide hydroxamic acid [SAHA]) [4,5], etc. However, most of these methods are unlikely to be highly effective and repeat treatment may be required.

Theory of allo-HSCT + TT

We have developed a new allo-HSCT method, HSCT + thymus transplantation (TT) from the same donor [6] (Figure 1). In the case of conventional allo-HSCT (left), the allo-T cells develop in the host thymus with education to achieve tolerance to the host. This results in a low GVT effect with minimal or no GVHD. In contrast, non-tolerant allo-T cells are externally supplied in the case of HSCT + DLI (right), resulting in a high GVT effect with strong GVHD. In the case of HSCT + TT (middle), not only allo-T cells, but also Treg cells, which preserve GVT activity while inhibiting GVHD [7], develop internally from the transplanted thymus [8]. This results in strong GVT with low GVHD in HSCT + TT. This new method is also effective in the treatment of several intractable diseases and conditions, such as autoimmune diseases in aging, advanced malignant tumors, exposure to supralethal irradiation, multiple organ transplantation from different donors, and type 2 diabetes mellitus, for which conventional methods are ineffective [6].

Effects of allo-HSCT + TT on tumors

We investigated the effects of allo-HSCT + TT in tumor-bearing mice (Table 1). In early tumors, although mice treated with allo-bone marrow transplantation (BMT) + DLI showed greater tumor regression than untreated controls and those treated with allo-BMT alone, strong GVHD also occurred and they died at an early stage. Interestingly, mice treated with allo-BMT + adult thymus transplantation (ATT) showed less GVHD than those treated with BMT + DLI, even with a comparable level of tumor regression [8].

We also examined the effects of BMT + ATT on leukemia [9]. In contrast to solid tumors, most mice treated with BMT + ATT or BMT + DLI showed almost complete remission of the tumor with long-term survival compared to those treated with BMT alone. However, the level of GVHD in those treated with BMT + ATT was significantly lower than in those treated with BMT + DLI. These results suggest that BMT + ATT may be effective in treatment of not only solid tumors, but also leukemia, without increased risk of GVHD.

Thymus atrophy is induced in hosts with advanced tumors, thus causing immunodeficiency, which is one of the major

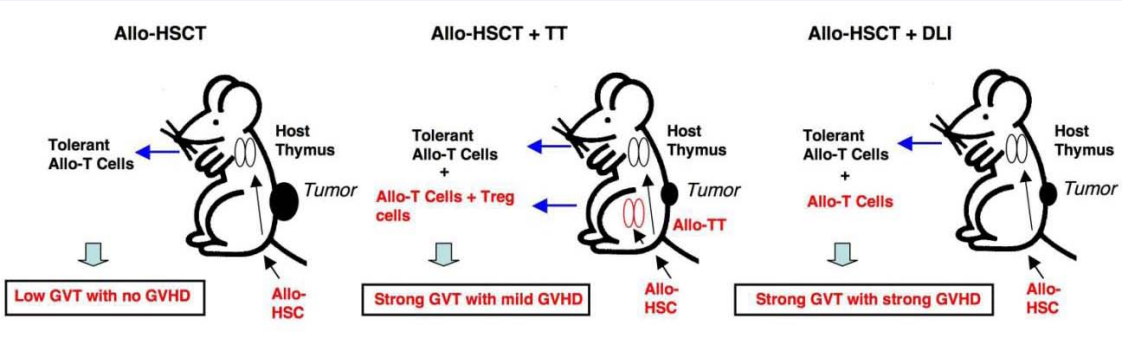

Figure 1 Theory of allo-HSCT+ TT for tumors. In the case of conventional allo-HSCT (left), the allo-T cells develop with tolerance to the host in the thymus. Low GVT effect with no/minimal GVHD is then induced. In the case of allo-HSCT + DLI (right), non-tolerant allo-T cells are supplied externally, and strong GVT effect with strong GVHD occurs. In the case of allo-HSCT + TT (middle), not only allo-T cells, but also regulatory T cells that preserve GVT activity while inhibiting GVHD, develop internally from the transplanted thymus. As a result, strong GVT with mild GVHD occurs.

Table 1: Effective allo-HSCT + TT for tumors compared with HSCT and HSCT + DLI. HSCT, hematopoietic stem cell transplantation; TT, thymus transplantation; ATT, adult thymus transplantation; NTT, newborn thymus transplantation; FTT, fetal thymus transplantation.

Disease	Mouse model	TT	Results	Reference
1) Early tumor with low GVHD	BALB/c with Meth-A sarcoma	ATT	Strong GVT	[8]
2) Advanced tumor Inhibition of lung metastasis	BALB/c with Meth-A sarcoma	FTT	Long-term survival with	[10]
3) Leukemia With low GVHD	B6 with EL-4 leukemia	ATT	Strong GVL	[9]

causes of death in such cases. We further examined the effects of HSCT + TT in mice bearing advanced tumors [10]. Although the thymus still atrophied in mice treated with allo-BMT + fetal thymus transplantation (FTT), the transplanted fetal thymus grew well. These mice showed longer-term survival than those treated with syngeneic (syn)- or allo-BMT alone, or syn-BMT + FTT with inhibition of lung metastasis. These findings suggest that HSCT + TT may also be effective for long-term survival in advanced tumors.

As the thymus shows functional differences with age, we also compared the effects of the thymus at three different ages (adult, newborn, fetus) [11]. Although HSCT + TT was superior to HSCT alone at all ages, newborn liver cell transplantation (NLT) as newborn HSCT + newborn thymus transplantation (NTT) showed better results than fetal liver cell transplantation (FLT) as fetal HSCT + FTT and BMT + ATT in these experiments. Although further studies are needed, these findings suggest that young thymus, as close as possible to newborn, may be preferable for such treatments.

Assignment for allo-HSCT + TT

Mice bearing tumors treated with HSCT+TT showed no lethal GVHD, and required no additional treatments with long-term survival. TT initially appears to represent a simple method, but may represent a significant approach to supplying the organ in which T cells are differentiated, produced, and functionally regulated to maintain homeostasis. Therefore, this method seems to have benefits compared to those outlined above. However, it is both ethically and technically difficult to obtain adequate thymus tissue for clinical use. In this respect, grafts could be obtained from patients with congenital heart diseases or from aborted fetuses, as utilized previously [12,13]. These materials are close to the preferred newborn thymus. In addition, a method for thymus regeneration and differentiation from stem cells has also been developed [14,15]. Therefore, HSCT + TT may become a viable strategy for the treatment of tumors as a valuable next-generation HSCT method.

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