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

Naoki Hosaka*

1Department of Pathology, Kansai Medical University, Japan
2Department of Clinical Sciences and Laboratory Medicine, Kansai Medical University, Japan

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 allo-reactivity 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
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.

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

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.

ACKNOWLEDGEMENTS

The author wishes to thank Prof. S. Ikehara of the Department of Stem Cell Disorders, and Prof. H. Takahashi of the Department of Clinical Sciences and Laboratory Medicine, Kansai Medical University, for support in this work.

REFERENCES


