

Mini-Transplantation Strategy for Solid Tumors

Yoichi Takaue

*Hematopoietic Stem Cell Transplant/Immunotherapy Unit, National Cancer Center Hospital,
Tokyo, Japan*

Abstract

In our phase I reduced-intensity stem cell transplantation (RIST) study with fludarabine (180 mg/m²) or cladribine (0.66 mg/kg) plus busulfan (8 mg/kg), with or without anti-thymocyte globulin (ATG), a total of 85 patients who had a variety of hematological (n=68) or metastatic solid tumors (n=17) were treated. This presentation will further update the results of our RIST program, highlighting several burning issues in the treatment of patients with solid tumors. Pathological classification of solid tumor in this program included renal cell carcinoma (RCC, n=8), rhabdomyosarcoma (n=2), malignant melanoma (n=2), neuroblastoma (n=2), osteosarcoma (n=1), alveolar soft-part-tumor (n=1) and cholangiocarcinoma (n=1). All received PBSCT from an HLA-identical or one antigen-mismatched relative. Regimen-related toxicities were mild and >90% donor chimerism was achieved before day 30 in a majority of patients. The overall survival for hematological and solid malignancies was the same ca. 70% at 1 year.

The rationale of cytoreductive regimen administered before hematopoietic stem cell transplantation (HSCT) has been to provide maximum antitumor effect by high-dose chemo/radiation therapy. However, recent observations in patients undergoing allogeneic HSCT support that total leukemia eradication by high-dose therapy is not mandatory. The recently introduced mini-transplantation or reduced-intensity HSCT (RIST) is based on the concept of intensifying immunosuppression to primarily enhance the engraftment of donor cells, rather than cytoreduction. Evidence has accumulated that stable engraftment can be achieved without myeloablation, when agents with potent immunosuppressive activities are used appropriately. Thereafter, established donor-derived lymphohematopoiesis provides a basis to exert antitumor effects: non-specific in terms of the production of cytokines which carry anti-tumor potency, or specific in terms of targeting to tumor-associated antigens or differences in the expression of minor histocompatibility antigens between the donor and host. Reported evidence of a graft-versus-tumor (GVT) effect against solid tumors has stimulated interest in the possible application of this procedure to a variety of solid tumors. The development of preparatory regimens for NST should consider the intensity of im-

mune suppression and the induction of complete donor cell-type chimerism. Additionally, satisfactory anti-tumor activity is required for the short-term control of tumors until a potent GVL effect emerges.

Although there has been growing international interest in NST, this is still in the very early phase of development and the efficient accumulation of expertise is urgently required, particularly with regard to graft-versus-host disease (GVHD)/GVT and feasibility of treating patients with solid tumors. The underlying immune mechanism involved in chimerism induction, GVHD and GVT is unclear, complex and disease-specific. Attempts have been made to intentionally induce the early occurrence of GVHD, which has been considered to be a marker of a GVT effect, through the omission or early withdrawal of prophylaxis for GVHD. However, it has become clear that the maximum induction of GVT does not necessarily rely on the clinical manifestation of GVHD. Hence, conditioning regimen and immunosuppressive strategy after RIST should be carefully balanced against the risk of GVHD and relapse of the basic disorder.

In our phase I RIST study with fludarabine (180 mg/m²) or cladribine (0.66 mg/kg) plus busulfan (8 mg/kg),

with or without anti-thymocyte globulin (ATG), which was performed between April 2000 and March 2002, a total of 85 patients who had a variety of hematological (n=68) or metastatic solid tumors (n=17) were treated. Pathological classification of solid tumor includes renal cell carcinoma (RCC, n=8), rhabdomyosarcoma (n=2), malignant melanoma (n=2), neuroblastoma (n=2), osteosarcoma (n=1), alveolar soft-part-tumor (n=1) and cholangiocarcinoma (n=1). All received PBSCT from an HLA-identical or one antigen-mismatched relative. Regimen-related toxicities were mild and >90% donor chimerism was achieved before day 30 in a majority of patients. The overall survival for hematological and solid malignancies was the same ca. 70% at 1 year.

In all 3 patients with non-clear cell type RCC, transient GVT effect was observed. One is too early for evaluation and remaining 4 patients with clear cell type RCC remain in stable disease. One patient with melanoma had stable disease past one year after transplant, although subsequently died of progressive disease on day 433. One of the 2 patients with rhabdomyosarcoma did not show any GVT effect even on grade III acute GVHD and died of progressive disease on day 56. In contrast, the patient with osteosarcoma showed evidence of clinical response when he developed grade IV acute GVHD. This presentation will further update the results of our RIST program and highlight several burning issues in this field for interactive discussion.