Nonmyeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Solid Tumors

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Abstract Nonmyeloablative allogeneic hematopoietic stem cell transplantation (allo–HSCT) is a new way to treat refractory solid tumors which is depended on the effects of graft versus tumor(GVT) effect to eradicate the malignant cells. Compared with high–dose myeloablative preparative regimen it has advantages of a low risk of treatment–related complications and mortality. So it is also eligible for patients who are too old or medically infirm for conventional allo–HSCT.

.**Key Words** Hematopoietic stem cell transplantation; GVT; Neoplasms/therapy

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective way to treat hematologic malignancies and some tumors. The high-dose chemotherapy and/or total body irradiation (TBI) is a traditional preparative regimen of allo-HSCT to treat hematologic malignancies. However, because of its high risk of transplant-related mortality (TRM), its application is restricted to some extent. Recently, researchers began to explore the use of relatively nontoxic, nonmyeloablative, or reduced-intensity preparative regimens still allowing the generation of GVT effect and reducing the TRM. Nonmyeloablative allo-HSCT is not only used to treat hematologic maligncies but also used to treat non–hematologic maligncies.

Myeloablative allo–HSCT

Conventional allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with marrowbased diseases, involve conditioning with very high doses of systemic chemotherapeutic agents with or without ionizing total body irradiation (TBI) to eradicate the patients´ underlying diseases and suppress their immune responses so they don´t reject the subsequent allografts. The allografts serve to ″rescue″ patients from the marrow lethal effects of the conditioning regimens[1]. High-dose myeloablative therapy with allogeneic hematopoietic stem cell transplantation is an effective treatment for hematologic malignancies and other malignant tumors. However, the research shows that it has a high treatment–related complications, ranging from 10% to > 50%, depending on histocompatibility, age comorbidities, and disease factors which restricts the use of it[2].

Nonmyeloablative allo–HSCT

Background and concepts In the research of myeloablative allo –HSCT, showed that many hematologic malignancies cannot always be eradicated by high doses of chemoradiation conditioning, even though the regimens may have been intensified to the levels at which serious organ toxicities are encountered [1]. Some studies demonstrated that relapse rates were markedly less in patients with graft-versus-host disease (GVHD) than that in patients without GVHD; subsequent studies found that relapse rates were lowest in patients who developed both acute and chronic GVHD, higher in those without GVHD, and highest in recipients of T–depleted stem cells or grafts from identical twins. The

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subsequent finding that complete remissions could be achieved in patients who had relapsed after transplantation by the infusion of viable donor lymphocytes provided further evidence for the existence and potency of a GVT effect[3-4]. In this condition it develops nonmyeloablative allo -HSCT which strengthenes the effects of GVT and reduces the intensities of preparative regimens.

Nonmyeloablative allo-HSCT means less toxic preparative regimens involving conditioning with low doses of systemic chemotherapeutic agents with or without total body irradiation (TBI) to suppress the patients´ immune system to achieve engraftment. Upon engraftment, the use of immunesuppressive chemotherapeutic drugs to suppress the activity of T cells derived from the donor derived cells to achieve mixed chimerism and allow development of GVT effects to eradicate the malignant cells. The post -transplantation infusion of donor lymphocytes is usually part of nonmyeloablative allo -HSCT protocols. DLIs are given to convert mixed to full donor chimerism and to promote GVT effects in non-responding patients [5]. Two general strategies have emerged [2]: ①the use of immunosuppressive chemotherapeutic drugs, usually a purine analog in combination with an alkylating agent ② the immunosuppressive effects of low-dose total body irradiation, alone or in combination with fludarabine.

GVT effects after nonmyeloablative allo -HSCT The aim of nonmyeloablative allo-HSCT is to increase the GVT effect to eradicate the malignant cells and reduce the intensities of the preparative regimens. The development of GVT effect usually coincides with or follows the development of GVHD. However, in certain cases, GVT effect is seen in the absence of GVHD. Some studies suggested that some patients developed GVT effects without the development of GVHD [1]. GVT effect can be divided into two aspects[6]: ① GVT depended on GVHD: distinct T cell populations recognizing tumor restricted antigens and/or antigens shared by both the tumor and normal tissues may be involved in these GVT effects, So GVHD and GVT are also developed together; ② GVT don´t depended on GVHD: Distinct T cell populations are only recognizing tumor or hematopoietic specialized antigens. Furthermore, natural killer (NK) cells, dendritic cells, lymphokine-activated killer(LAK) cells and cytokine factors[7-8] are also related to the development of GVT effect. Effective strategies to separate GVHD from GVT are critical for the success of nonmyeloablative allo-HSCT. Several approaches have been attempted[9], including full-dose tacrolimus and methotrexate, shorter courses of these agents, and a combination of CSA and MMF. Acute GVHD seems to be less severe following a nonmyeloablative regimen compared to conventional myeloablative therapy, but most patients will develop GVHD after discontinuation of immunosuppressive therapy, leading to severe complications. Results of a previous study suggested that the use of Campath-1, an anti-CD-52 monoclonal antibody, may decrease the incidence of GVHD, but its long-term effect on GVT and recovery of the immune system remains to be determined. Other experimental approaches to separate GVT from GVHD have been suggested, including transplantation of a T-cell-depleted graft, selected CD34-cells followed by infusion of either engineered T or NK cells targeting the malignancy, or donor T cells transduced with a suicide gene such as herpes simplex virus thymidine kinase, followed by the administration of acyclovir to kill these cells if severe GVHD occurs.

Advantages, Limitations and Feasibilities of nonmyeloablative allo-HSCT

Advantages[1] Nonmyeablative preparative regimens have been studied as a means to reduce regimen related toxicity in patients considered ineligible for myeloablative preparative regimens because of advanced age or comorbidities. It may also reduce the incidence and severity of acute GVHD, since its clinical manifestations partly result from the toxicity of the preparative regimen and subsequent cytokine release as well as the alloreactivity of the graft. Residual host T cells may also inhibit development of GVHD. Infectious complications may also be reduced. In addition, since the nonmyeablative preparative regimen does not immediately eliminate host derived immunocompetent cells, these cells can contribute to host defense in the early post-transplant period. Nonmyeloablative preparative regimen is a safe way for patients who are too old or medically infirm to qualify for conventional allo-HSCT because of its low doses of chemotherapy or radiotherapy and low toxicities to organs.

Limitations ①Requirement for an HLA-matched donor. Because of the polimorphism of the system of HLA antigens, it is not easy to find a HLA-compatible donor. ②Transplant-related toxicity: Though the transplant-related toxicity is reduced

obviously compared with the myeloablative preparative regimens, the incidence is still to 10%~20%. ③ Because of the mixed-chimera after the non-myeloablative preparative regimens and the use of immunosuppressive drugs for preventing GVHD (eg. CSA), delay the generation of GVT effect. So patients with rapidly progressive diseases are unlikely to benefit from the use of nonmyeloablative allo-HSCT. ④ Not all solid tumors have the same level of sensitivity (RCC and ovarian carcinoma have a high sensitivity and the sensitivity of melanoma is low). ⑤The tumors with high malignance is unlikely to be controlled, which suggested pre-graft tumor kinetics must be slowed down.[10]

Indications[6] ①Progressive metastatic disease ② Expected survival of patient is over 6 months ③In vitro or clinical evidence that tumor is susceptible to immune-attack ④Absence of central nervous system involvement ⑤HLA-compatible sibling available ⑥Tumor´s volume is small and with slow proliferative kinetics.

Clinical Trials

Metastatic renal cell carcinoma Childs et al[11-12] firstly reported that the preparative regimens by using the cyclophosphamide (60 mg/kg × 2d) and fludarabine (25 mg/m^2 × 5d), and were then transplanted with stem cell allograft from their HLA identical or single antigen mismatched sibling donor to treat 19 patients with renal cell carcinoma. Cyclosporin (CSA) alone or in combination with mycophenolic acid (MMF) was used as graft versus-host disease (GVHD) prophylaxis and was withdrawn as early as day 30 in patients with mixed T-cell chimerism or disease progression. Results: Ten of the 19 patients had regression of metastatic disease compatible with a GVT effect. Ten patients had been observed with acute GVHD(53%) and one case of them died. Two patients died of transplant-related causes. The observation of GVT effects in RCC led us to initiate similar trials of non-myeloablative allo-HSCT for patients with a variety of different treatment-refractory solid tumors.

Metastatic breast cancer Bregni et al[13] reported that the preparative regimens by using thiotepa (10 mg/kg), cyclophosphamide (30 mg/kg) and fludarabine (30 mg/m^2) and then were transplanted with stem cell from allograft from their sibling donor for six patients with progressive metastatic breast cancer. CSA and short-course MTX were used for acute GVHD prophylaxis. Patients who had stable or progressive disease after the withdrawal of CSA and had no evidence of GVHD were eligible to receive up to three infusions of DLI. Patients who had no response to DLI and no GVHD were eligible to receive low-dose subcutaneous interferon alpha. Results: One patient was died of rapid progression after 109 day. DLIs were given to five patients with diseases progressing after allografting, and three patients after two infusions followed by IFN-α. Two patients had partial remission and three patients had progressive disease. One patient remained stable disease. All living patients achieved clinical remission or stabilization of their disease. Regression of metastases was delayed and was always linked to full chimerism achievement and acute/chronic GVHD. Uneo[14] et al had the same reports. These results demonstrated that it is feasibility for patients with advanced metastatic breast cancer to treat with nonmyeloablative allo-HSCT.

Ovarian Bay[15] et al reported that four patients with malignant ovarian tumors resistant to chemotherapy underwent allogeneic transplantation received a non-myeloablative regimen. All donors were HLA-identical siblings. Results: Three patients presented acute or chronic GVHD with tumor regression at least 50%. These tumor regressions were measured by CA-125 levels and CT scans. One patient died of rapid progression just after transplantation and one patient died of GVHD after 127 days. DLI seemed to promote GVHD which was able to control disease progression. The number of cases presented is small, however, and clinical experience on a larger scale will be required to determine the real clinical efficacy of graft versus cancerous ovarian cells.

Pancreatic cancer and other tumors Takahashi[16] et al reported that the nonmyeloablative preparative regimens by using the cyclophosphamide (60 mg/kg) and fludarabine (25 mg/m^2) and then were transplanted with stem cell from allograft from their HLA identical sibling donor to treat five patients with unresectable pancreatic cancer. Cyclosporine was used for GVHD prophylaxis. Results: Complete donor T-cell chimerism in peripheral blood was obtained in four patients on day 15 after transplantation. Two patients had tumor reduction as determined by CT, tumor markers in two patients decreased, symptom relieved in three patients. Four

patients developed acute or chronic GVHD. Administration of immunosuppressive drugs for the treatment of GVHD resulted in the elevation of tumor marker levels. Omuro [17] et al reported that a 59-year-old female with an unresectable, large pancreatic tumor underwent nonmyeloablative allo-HSCT from her HLA-identical sibling. Pronounced tumor regression and relief from pain without acute GVHD were observed following transplantation. The patient survived more than 300 days after transplantation with extensive chronic GVHD, and has tumor regression with an 80% reduction in tumor size. Pedrazzoli [18] et al reported that the nonmyeloablative preparative regimens by using the fludarabine (30 mg/m^2) and cyclophosphamide (30 mg/kg) and then were transplanted with stem cell from allograft from their HLA identical sibling donor to treat three patients with sarcoma that were not amenable to further conventional treatment. Results: One patient had partial remission and two patients had stable diseases. Zetterquist [19] et al. reported that one patient with colorectal cancer received nonmyeloablative allo-HSCT from his HLA-identical sibling as the only treatment. The patient died of pneumonia and cardiac insufficiency four months after transplantation. The necrosis of most of the tumor cells was found at autopsy. Hentschke [20] et al reported that nonmyeloablative allo-HSCT could induce an antitumor effect in patients with colon cancer and adenocarcinoma.

CONCLUSION

Though there are many exciting results about nonmyeloablaive allo-HSCT to treat solid tumors [21], the use of nonmyeloablative allo-HSCT to treat solid tumors, the mechanism of which is the effects of GVT, is in its infancy. Compared with the traditional myeloablative allo-HSCT it has a low risk of transplant-related complications and low mortality, so it is especially applicable to the patients who are too old and medically infirm to qualify for conventional allo-HSCT. However it comes up with many problems such as the prevention of GVHD, the enhancement of GVT effects, and the evaluation of the long-term efficacy of it deserved to be investigated in the future. We can not deny that it is one of the efficient ways to treat the treatment-refractory solid tumors.

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