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MINIREVIEWS

Review of allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning in solid tumors excluding breast cancer

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Abstract

Solid tumors in adults constitute a heterogeneous group of malignancy originating from various organ systems. Solid tumors are not completely curable by chemotherapy, even though some subgroups are very chemo-sensitive. Recently, oncologists have focused on the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) with reduced intensity conditioning (RIC) for the treatment of some refractory solid tumors. After the demonstration of allogeneic graft-versus-leukemia effect in patients with hematological malignancies who received allo-HSCT, investigators evaluated this effect in patients with refractory metastatic solid tumors. According to data from experimental animal models and preliminary clinical trials, a graft-versus-tumor (GvT) effect may also be observed in the treatment of some solid tumors (*e.g.*, renal cell cancer, colorectal cancer, *etc*.) after allo-HSCT with RIC. The use of RIC regimens offers an opportunity of achieving full-donor engraftment with GvT effect, as well as, a reduced transplant-related mortality. Current literature suggests that allo-HSCT with RIC might become a choice for elderly and medically fragile patients with refractory metastatic solid tumors.

Key words: Renal cell carcinoma; Allogeneic hematopoietic stem cell transplantation; Colorectal cancer; Ovarian cancer; Sarcoma

Core tip: Some refractory metastatic solid tumors including renal, ovarian and even colon cancers may respond well to allogeneic hematopoietic stem cell transplantation (allo-HSCT) with reduced intensity

conditioning (RIC). Their lower toxicity profiles and lower non-relapse mortality rates constitute the advantages of RIC. The use of allo-HSCT with RIC or non-myeloablative regimens can be a feasible option among fragile patients, such as geriatric patients and patients with comorbidities. Future studies are needed for a clear-cut understanding of the mechanisms of graft-versus-leukemia and graft-versus-tumor effects of donor T-cells and their subsets in order to optimize the efficacy of such treatment modalities in patients with refractory solid tumors.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is primarily used in patients with relapsed or high-risk hematologic malignancies and the efficacy of this treatment has been substantially demonstrated. The first allo-HSCT in the literature in a patient with a solid tumor was published in late 90s[1]. The principles of allo-HSCT consist of maximal tumor cytoreduction with high-dose chemoradiotherapy and adequate immunosuppression in order to provide engraftment of donor stem cells, as well as graft-versus-tumor (GvT) effect[2]. Studies investigating high dose chemotherapy with autologous stem cell rescue in patients with solid tumors yielded controversial and disappointing results[3-7]. This has led to the development of novel approaches, including allo-HSCT with reduced intensity conditioning (RIC) regimens, which aim to create and take advantage of a GvT effect in order to induce more durable responses[1,2,8-10]. Today, types of conditioning regimens that are used prior to allo-HSCT include myeloablative (MA), RIC and non-myeloablative (NMA) regimens. MA regimens lead to irreversible cytopenia and therefore, stem cell support is needed. In contrast, NMA regimens cause minimal cytopenia and can be given without stem cell support. RIC regimens do not completely fit in the criteria for MA and NMA regimens. The marrow aplasia is reversible; however, stem cell support is mandatory.

NMA/RIC regimens for allo-HSCT have introduced a new era for treating elderly and those with comorbidities[11-13]. The RIC regimens are currently being used for as much as 40% of all allo-HSCTs and becoming increasingly popular. The growing knowledge on the immune system and T-cell biology has made allo-HSCT a promising approach for the treatment of some solid tumors. Several phase Ⅰ and Ⅱ studies, which were conducted by the European Society for Blood and Marrow Transplantation Solid Tumors Working Party (EMBT-STWP) documented the presence of a GvT effect in patients with various solid tumors, such as renal, ovarian and colon cancers and soft tissue sarcomas[2].

This novel strategy provides a switch from a chemotherapy-based to an immunotherapy-based approach[14]. Replacing conventional MA regimens with NMA/RIC regimens prior to allo-HSCT has two main goals: (1) to diminish the high transplant-related morbidity and mortality[15-19]; and (2) to induce allo-reactivity against the metastatic solid tumor *via* a GvT effect[1,12].

The successful engraftment rates together with a lower transplant related mortality (TRM) and the presence of GvT effect made allo-HSCT with RIC an attractive option for the treatment of several solid tumors within the last decade[20-24]. The lower toxicity obtained by the reduction of chemoradiotherapy dose also enables allo-HSCT with RIC to become a choice for the elderly and medically fragile patients with metastatic solid tumors[1,12]. This review briefly describes the background, rationale, and clinical results of allo-HSCT with RIC as an immune-based strategy *via* GvT effect for the treatment of some metastatic solid tumors, including renal cell carcinoma (RCC), metastatic colorectal cancer (mCRC) and ovarian cancer.

CYTOTOXIC ADOPTIVE T-CELL THERAPY

Advances in systemic therapy for metastatic cancer have focused on important cellular pathways with critical roles in cancer development and progression[25]. Although a dramatic success is obtained in the minority of patients, this approach provides a relatively short-term benefit in the majority and exposes them to chronic toxicities, including cardiac and dermal toxicities and thus, is not cost-effective[26].

The mechanisms during the evasion of adoptive immune system by tumor cells have been described as growth, angiogenesis and tissue remodeling. During this process, the tumor cells also exploit the innate inflammatory response. Besides these mechanisms, the role of tumor microenvironment is also regarded as a new target for therapy[27]. Advances in understanding of cancer immunology and especially the role of the adoptive immune system, have identified new targets for the treatment of solid tumors[27].

The term, adoptive T-cell therapy (ATCT), involves the expansion of cytotoxic immune effector cells. It may be either specific or non-specific[25]. The GvT effect and tumor response after allo-HSCT with RIC may be regarded as a non-specific ATCT, as it involves leukocyte-activated killer cells (LAKs) and cytokine-induced killer cells (CIKs), which are described and discussed in this paper. ATCT is not yet considered as a standard treatment modality in the medical oncology practice. However, it is considered as the most potent immunotherapeutic approach according to the results of some early phase trials[27].

GVT EFFECT

The effect of immune system in inducing tumor regression is well-described. Graft-versus-host disease (GvHD) that occurs after allo-HSCT contributes to and maintains an anti-leukemic effect[28]. Thus, it is referred as graft-versus-leukemia (GvL) effect. This effect was first demonstrated with the eradication of leukemia in mice receiving non-syngeneic allogeneic transplant after irradiation[29]. Since then, several direct and indirect evidences of GvL effect after allo-HSCT have been reported. The GvL effect is generally associated with GvHD[30]. A stronger GvL effect is observed in chronic GvHD than in acute GvHD[31]. The probability of being in remission is also higher in patients with GvHD when compared to patients without GvHD[32]. Other strong evidences for the presence of an immune-mediated GvL effect are the significantly increased relapse risk in patients receiving T-cell depleted transplants and the lower risk of relapse observed in patients undergoing allo-HSCT rather than autologous HSCT[2,33-36]. The direct evidence of GvL effect comes from the studies reporting that donor lymphocyte infusions (DLI) given after transplant might augment the GvL effect of allo-HSCT and DLI infusion without cytotoxic therapy might induce and maintain remission in patients who relapse after allo-HSCT[37-40].

The GvL effect, which eradicates malignant cells *via* fas-dependent killing and perforin degranulation, is mediated by donor T cells ($CD4^+$, $CD8^+$ and natural killer - NK-cells)[41,42]. The major cytokines that potentiate the GvL effect include interleukin-2 (IL-2), interferon-C and tumor necrosis factor-α[43]. Post-transplant adoptive therapy with cytotoxic T-lymphocytes (CTLs) against human cancer-associated antigens, minor histocompatibility antigens (*e.g.*, HA-1, HA-3, *etc.*) or T-cell receptor genes may be used to induce anti-tumor effects[44]. The development of acute and chronic GvHD has been linked to a better response to therapy in solid tumors[2]. Identification of antigen targets of GvT and development of targeted therapies may further improve the immune effect of allo-HSCT for solid tumors and reduce the treatment toxicity[2].

Allo-HSCT is an immuno-modulatory therapy aiming at exploiting a GvT effect. However, it has to be emphasized that a delicate balance between effective immunosuppression, GvHD and relapse should still be considered.

Allo-HSCT with RIC in renal cell carcinoma

RCC is a common malignancy diagnosed in patients older than 50 years of age and almost one third of cases are metastatic at the time of diagnosis[45]. Despite various treatment strategies including hormonal therapy, chemotherapy and immunotherapy, the prognosis of metastatic RCC is extremely poor with a median survival of 10 mo and a 5-year survival of less than 5%[46,47]. RCC is sensitive to immunotherapy. Interferon-α with or without IL-2 (especially at high doses) have been widely used. However, the rates of response (10%-20%) and long-term progression- free survival (4%-15%) are still unsatisfactory[48-50]. Allo-HSCT with RIC is considered as a promising option in this setting[11,13].

A response rate of 53% has been reported in the first series of allo-HSCT with NMA conditioning for cytokine-refractory RCC[11]. Another trial included 75 metastatic RCC patients and reported a sustained engraftment in 74 out of 75 patients after allo-HSCT with NMA conditioning[51]. In this study, chronic GvHD was observed in 50% and was associated with a significant tumor response.

The largest series of allo-HSCT with NMA conditioning in RCC patients was published by the EBMT-STWP, in which a fludarabine-based conditioning regimen was administered to all 124 patients prior to peripheral blood allo-HSCT[52]. Engraftment failure was observed in 2.4%. TRM at the end of first year was 16% and associated mostly with acute GvHD. A response rate of 22.5% was achieved including complete response in 4 patients at a median of 150 (42-600) dpost-transplant.

Nowadays, patient selection for allo-HSCT has become an important issue, since disease progression after transplantation is more frequent among patients with rapidly progressive tumors. In order to determine which patients benefit most from allo-HSCT, 70 patients who underwent allo-HSCT were evaluated according to pre-transplant characteristics, such as performance status, C-reactive protein and lactate dehydrogenase levels in a study conducted by EBMT. This study suggested that these parameters could be used to stratify patients with advanced RCC who are candidates for allo-HSCT and to assist clinicians in decision-making and selection of an appropriate treatment program. As a result the patients with good prognostic criteria had a longer median survival than those with poor prognostic criteria, 23 mo *vs* 3.5 mo, respectively[45]. Another study reported a higher response rate in the presence of an early transplantation, HLA-mismatched donors, higher Karnofsky score, lower number of metastatic sites and limited chronic GvHD[52]. Currently, some other scoring systems are also developed for predicting survival in previously treated RCC patients[46].

In conclusion, NMA conditioning followed by allo-HSCT in patients with RCC is feasible and it might prolong survival, especially in patients with favorable prognostic characteristics.

Allo-HSCT with RIC in colorectal cancer

Inoperable metastatic colorectal cancer (mCRC) is an incurable disease. Despite advances in therapy, median survival with fluorouracil-leucovorin, irinotecan, and oxaliplatin as first-line therapy is 18 to 22 mo and in case of resistance to these agents, the median survival declines 9 to 12 mo with second-line chemotherapy[53,54]. Combination of chemotherapy with monoclonal antibodies such as cetuximab or bevacizumab improves remission rates and survival; however, long- lasting remission usually cannot be achieved, especially in the presence of resistant disease[55,56].

Allo-HSCT following RIC has emerged as a novel

immunotherapy-based therapeutic strategy for the management of mCRC[15,57,58]. In a study including six advanced mCRC patients, one complete response and one mixed response, including regression of lung and lymph-node metastasis and progression of liver metastasis were obtained[59]. In a multicenter EBMT trial, among 39 patients with progressive mCRC overall disease control was achieved in 18 (46%) and 1 complete (2%), 7 partial (18%), and 10 stable disease responses (26%) were reported after allo-HSCT[60]. Allo-HSCT with RIC might be an alternative to conventional strategies, especially in young patients with refractory mCRC.

Allo-HSCT with RIC in ovarian cancer

Ovarian cancer (OC) is the most fatal gynecologic malignancy and the fifth-leading cause of death among women in the developed countries[61]. Despite extensive surgery and use of new generation drugs such as taxanes (mostly in combination with carboplatin), relapse rates may reach up to 50%. Although sensitive to high-dose chemotherapy (especially based on carboplatin combinations), the median overall survival is about 2 years for relapsing disease[62,63]. The only benefit of high-dose chemotherapy does appear to be delayed relapse[64,65].

In a study, including five refractory OC patients who underwent allo-HSCT with RIC, tumor regression were observed in four patients during acute or chronic GvHD and relapse occurred in one patient treated with methylprednisolone for chronic GvHD[66]. A retrospective study from the EBMT-STWP database included 17 heavily pre-treated OC patients and mortality was reported in 11 patients, 8 of which were due to tumor progression at a median follow-up of 296 d (5-1599)[67]. Grade 2-4 acute GvHD was reported in eight patients, seven (41%) of which had a partial response. Tumor regression was achieved in one out of three patients who received DLI. This data supports the existence of a graft-versus-ovarian cancer effect in correlation with GvHD. In another retrospective multicenter study with 30 allografted OC patients, objective response was observed in 50% and TRM was 20% at the end of first year[68]. The median overall survival was 10.4 mo with a median follow-up of 74.5 mo (16-148). Overall survival was significantly higher among patients with chronic GvHD (17.6 mo *vs* 6.5 mo, $P < 0.05$).

Allo-HSCT with RIC for OC could be a feasible treatment option. However, supporting data are limited.

Allo-HSCT with RIC in soft tissue sarcomas

Soft tissue sarcomas (STS) constitute a rare and heterogeneous group of malignant tumors, which include less than 1 percent of all adult malignancies. Prognosis of STS is poor with a median survival of about 1 year with conventional treatments[69].

In experimental animal models of allogeneic transplantation, immune-mediated effect against sarcoma has been shown[70,71]. However, reports on STS treated with allo-HSCT mostly consist of single case reports and small series of patients from HLA-matched sibling donors. Although some authors have reported the evidence of a graft-*vs*-sarcoma effect, no evidence of cancer regression following allo-HSCT with RIC regimens were reported among patients with various histologic subtypes[72-74]. In a retrospective study, 14 adult patients from EBMT database with advanced STS received allo-HSCT with RIC for chemo-refractory disease, excluding rhabdomyosarcoma (most frequently a pediatric disease with an extremely different natural history) and they were assessed regarding whether a GvT effect could be generated in this setting. TRM was reported in two patients and progressive disease was observed in eight patients. Four patients experienced long-lasting disease stabilization following allo-HSCT. Authors concluded that an immune-mediated effect cannot be excluded in some STS[75].

In conclusion, allo-HSCT with RIC may give rise to some degree of significant responses in some refractory metastatic solid tumors, such as renal, ovarian and even colon cancers. The advantages of RIC regimens are their lower toxicity profiles and lower non-relapse mortality rates. Allo-HSCT with RIC or NMA can be a feasible option for geriatric patients and patients with comorbidities. Future studies are needed for a clear-cut understanding of the mechanisms of GvL and GvT effects of donor T-cells and their subsets in order to optimize the efficacy of such treatment modalities in patients with refractory solid tumors.

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