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Use of Monoclonal Antibodies in Conditioning Regimen in Transplantation

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Abstract

Monoclonal antibodies (MoAbs) alone or in the combination of conventional therapies have been used in the treatment of many benign or malignant diseases. In the transplantation setting, MoAbs have been generally applied as a part of conditioning regimen in the aims of the prevention of graft versus host disease and/or graft failure or treatment of underlying hematologic disease. The most frequent used moAbs for this purpose are rituximab, alemtuzumab, Gemtuzumab Ozogamicin or radioimmunoconjugates. In this chapter, we discussed the role of moAbs use in the conditioning regimens of allogeneic or autologous stem cell transplantation.

Keywords: Monoclonal antibodies, Conditioning Regimen, Stem Cell Transplantation

1. Introduction

Monoclonal antibodies (MoAbs) to treat a variety of benign and malignant diseases are used alone or in combination with conventional therapies. The use of MoAbs in autologous and allogeneic hematopoietic stem cell transplant (allo-HSCT) is subject to the following conditions for:

1. In vivo purging of graft and as a part of the conditioning regimens in the autologous or allogeneic HSCTs, and/or
2. Prevention or treatment of graft versus host disease (GvHD) developed after allo-HSCT.

The goals of the use of the MoAbs for in vivo purging of graft and/or as a part of conditioning regimens in autologous or allogeneic HSCTs are to obtain tumor-free stem cells, to reduce the recurrence, and to provide the resulting increase in the efficacy of transplantation on the

underlying disease and the cure rate. Additionally, MoAbs in allo-HSCTs prevent the graft rejection and/or reduce the frequency and severity of GvHD. More frequently used MoAbs in the transplantation are: Rituximab, Radioimmunotherapeutics (RITs), Alemtuzumab, and Gemtuzumab Ozogamisin.

2. Rituximab

Rituximab, the chimeric anti-CD20MoAb is mostly used to treat a broad variety of B-cell non-Hodgkin's lymphomas (NHL). Rituximab shows direct activity or complement-mediated cytotoxicity and antibody-dependent cytotoxicity. There are numerous studies on the use of conditioning regimens in autologous and allogeneic HSCTs settings.

The first study was reported by Flinn *et al.* [1] including 25 patients with a variety of NHL (11 follicular lymphoma, 7 mantle cell lymphoma, 5 chronic lymphocytic leukemia or small lymphocytic leukemia, 1 lymphoblastic lymphoma, and 1 marginal zone lymphoma). In this study rituximab was used for in vivo purging during the stem cell mobilization with cyclophosphamide (Cy) and also added in the myeloablative (MA) conditioning regimen including mostly Cy plus total body irradiation (TBI) and a further dose given after the engraftment. As a result, rituximab was well tolerated, engraftment was fast, and temporary neutropenia developed in the mean of 99.5 days in six patients but clinically significant infection was not reported.

Following study on the addition of rituximab for the conditioning regimen in autologous HSCT has been published by Flohr *et al.* [2]. In this phase II study, 27 patients with a variety of B-cell NHL in both the first day of the stem cell mobilization with chemotherapy and in the conditioning regimen, -10 and -3 days at the dose of 375 mg/square meter (sqm) rituximab have been used. The overall response rate has been reported as 96%. In the median follow-up of 16 months, disease free survival (DFS) and overall survival (OS) have been estimated as 77% and 95%, respectively. Another study of Khouiri *et al.* [3] have evaluated the efficacy of rituximab use in the stem cell mobilization and after the transplantation in a total of 67 patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). Rituximab (375 mg/sqm) was infused 1 day before chemotherapy and again administered 7 days after chemotherapy at 1000 mg/sqm. In addition, rituximab has been given to the patients on the first and eighth day of 1000 mg/sqm dose following the high-dose BEAM conditioning regimen for autologous HSCT. The results were retrospectively compared with those of a historical control group (n=30 patients) receiving the same preparative regimen without rituximab. Although neutrophil engraftment in the rituximab arm was late in a statistically significant proportion (median 10 days vs. 11 days, $p < 0.05$), similar incidence of infection has been shown in the patients who received rituximab compared with the control arm. In the median 20 months of follow-up, they reported that the possibilities of progression-free survival (PFS) and OS significantly prolonged in rituximab arm (PFS: 43% versus 67%, $p = 0.004$; OS: 53% versus 80%, $p = 0.002$). In a multicenter study from 10 centers associated with the Italian group, the *Gruppo Italiano Terapie Innovative nei Linfomi*, when retrospectively compared the high-dose therapies

with and without rituximab in the patients with DLBCL and FL undergoing autologous HSCT, either as salvage or as first-line therapy for high-risk presentation, rituximab was administered in four doses during the high-dose therapy immediately before peripheral blood collection to exploit the drug's in vivo purging effect, and two additional doses were usually used after autologous-HSCT. They found the similar response rate and early transplant-related mortality between rituximab (+) and (-), but the 5-year projected PFS and OS were better in those with rituximab (+) ($p < 0.0001$) [4].

Hick *et al.* have also evaluated the use of rituximab in 23 patients with relapsed FL during the mobilization of stem cells for in vivo purging and during the 8th and 24th week after autologous HSCT for a four-week maintenance treatment protocol [5]. This study showed that rituximab provided permanent molecular remission in 77% of the patients associated with significantly prolonged PFS versus those with continued polymerase chain reaction PCR positivity.

Many single-arm phase II studies including small number of patients have been reported that the addition of rituximab especially reduced intensity conditioning (RIC) regimens in allogeneic HSCT settings reduced the incidence of acute or chronic GvHD and non-relapse mortality (NRM) [7-11]. In these studies, rituximab has led to an increase of serious infections due to long-term cytopenias and prolonged hypogammaglobulinemia.

Ultimately, there is no consensus regarding the dosage and scheme of rituximab use as a part of conditioning regimen for autologous and allogeneic HSCT in these studies. In addition, it is also not sufficient in randomized controlled trials demonstrating the superiority of adding rituximab. Therefore, prospective multicenter randomized trials aiming to determinate the exact role of rituximab for in vivo purging and/or as a part of conditioning regimens should be made in lymphoma patients.

3. Radioimmunotherapeutics

Radioimmunotherapeutics (RITs) uses monoclonal antibodies directed against specific tumor antigens labeled with a particle emitting radioisotope to deliver radiation directly to the tumor. This type of treatment gives a high dose of radiation to tumor tissue and protects uninvolved tissues and organs [12-13]. Labeled antibodies to the antigen over-expression in the target tissue with radioactive substances specifically bind. For this purpose beta particles are the most frequently used: Radioactive particles connected the MoAb slowly give out its radiation and kill the other nearby cells. This is called as cross fire. They give high tissue distribution with high nucleotides in the target tissue and homogeneous energy and provide the myeloablation or affect the large tumor mass. To achieve a favorable biodistribution of a radiolabeled monoclonal antibody, an ideal antigen would be expressed homogeneously on the tumor cell surface and would lack expression on normal cells. Lacking such an antigen, methods to target lineage-specific hematopoietic antigens, such as CD20, CD33, and CD45, have been successfully developed in the autologous and allogeneic-HSCT setting.

Currently there are two RITs in clinical use for indolent NHL [14]: Yttrium-90 ibritumomab tiuxetan (^{90}Y -IT) (Zevalin) and iodine-131 tositumomab (^{131}I -T) (Bexxar). There are studies on the use of high or standard doses as a part of the conditioning regimen for the transplantation.

3.1. High-dose RITs

Studies are generally on the use of single or combined with chemotherapy in the conditioning regimen for autologous-HSCT. In the first study, Press *et al.* conducted the phase I study in 43 relapsed B-cell lymphoma patients, and the administration of anti-CD20 and anti-CD37 antibodies labeled ^{131}I -T alone in the conditioning regimen was to evaluate the toxicity and efficacy (15). The maximum tolerated dose was 27.25 Gy. However, researches have shown that patients administered more than this dose had cardio-toxic effects. In addition, the biodistribution of the antibodies in the patients with the large spleen size and a large tumor mass were emphasized not to be good in the study. The overall response rate of 95% with high-dose RIT (84% complete response and 11% partial response) and tumor response were calculated as the median of 11 months. Subsequently, the same researchers have made a phase II study with anti-CD20 labeled ^{131}I -T in 25 patients with relapse NHL [16]. In this study, they have reported that PFS was 62% and 93% of OS with the median 2-year follow-up. Similarly, Liu *et al.* found a median PFS of 42% and 68% of OS in median 42-month follow-up [17]. This was followed by similar studies regarding the use of the high-dose RITs. However, due to the gamma radiation emitted by ^{131}I -T most subsequent studies had been conducted with ^{90}Y -IT, a pure beta emitter [18-21]. There was no need to prolong strict patient isolation and contact alert in ^{90}Y -IT in contrast to ^{131}I -T. Besides, disease statuses prior to the transplantations in those studies were also variable. Although the use of high-dose RIT was planned for the patients unable to tolerate high-dose treatment, the majority of patients in the studies was under 60 years of age and had *chemosensitive* relapses. Additionally, there are no prospective studies to prove RITs' superiority to chemotherapy and/or radiotherapy. Furthermore, this treatment should be administered in specialized centers.

3.2. Standard-dose RITs

To overcome the problems related to the safe yield of high-dose RITs, the efficacies of standard-dose RITs combined with chemotherapy in preparative regimens of the transplantation have been assessed in the following studies. The results in several single-arm studies not including control group were impressive. In a randomized trial, the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 0401 in which ^{131}I -T-BEAM or Rituximab-BEAM were given to the patients with *chemosensitive* relapse of DLBCL [22], disease control and survival effects of RIT could not have been shown. A randomized study compared ^{90}Y -IT-BEAM with BEAM alone in recurrent B cell NHL was closed early by reason of the slow patient recruitment. As their evaluation with a small number of cases, it was the first randomized study that proved that higher DFS and OS were in the RIT arm. Nevertheless, the published studies do not support the routine use of standard-dose RITs in DLBCL.

Some studies in *chemorefractory* DLBCL patients who underwent autologous-HSCT conditioned by standard-dose RIT have been reported as two or three year PFS and OS 39%–63%

and 55%–67%, respectively [23-26]. In the European Mantle Cell Network MCL-3 study ^{90}Y -IT was given to patients younger than 66 years one week prior to BEAM or BEAC (Carmustine, Etoposide, Cytarabine and Cyclophosphamide) conditioning regimen [27]. When compared with the results of the MCL-2 study, they concluded that there was no benefit in the patients undergoing autologous-HSCT as a first-line intensification treatment.

In allogeneic HSCT, RIT has generally been added to the RIC regimens in the refractory NHL patients. One of the first studies where Shimoni *et al.* gave ^{90}Y -IT with fludarabine-based conditioning regimens to 12 patients with *chemorefractory* CD20+ NHL demonstrated the safety of RIT [28]. Subsequently, several studies related to adding RITs to the conditioning regimen have been published [29,30]. Although allogeneic HSCTs made by adding RITs to RIC regimes have reliability in these studies, it has not been shown to be superior to the transplantations with RIC regimens not including RIT yet.

There are some studies related to the adding of RITs to the preparative regimens in acute leukemia and myelodysplastic syndrome (MDS) as well. Initially, ^{131}I -labeled M195, the mouse Moabs of lintuzumab (reactive with CD33) was used in 10 patients with relapsed or refractory acute myeloid leukemia in a phase I study from the Memorial Sloan Kettering Cancer Center [31]. Subsequently, ^{131}I -labeled anti-CD33 MoAbs were added to standard myeloablative regimen in 31 patients with refractory or relapsed AML (n=16), accelerated or blastic phase chronic myeloid leukemia (CML) (n=14) or advanced myelodysplastic syndrome (MDS) (n=1) underwent allogeneic HSCT from their related donor [32]. The median survival was calculated as 4.9 months (range 0.3–90+ months). Three patients with relapsed AML remain in complete remission more than 5 years.

Based on the feasibility of MoAbs, investigators have focused on the CD45, the other antigen. The CD45 antigen, common leukocyte antigen, is expressed on the surface of virtually all hematopoietic cells, except mature red cells and platelets. In addition, CD45 expression has been detected in 85% to 90% of AML and ALL, and the antigen does not internalize after the antibody binding. In a phase I study conducted by the Fred Hutchinson Cancer Center, RIT with ^{131}I -anti-CD45 has been implanted one week prior to the conditioning regimen including Cy-TBI in AML beyond the first complete remission (CR), acute lymphoblastic leukemia, and MDS-excess blast [33]. The patients of this study have undergone allogeneic HSCT from their human leukocyte antigen (HLA) -identical relative donors or autologous HSCT. This first study has shown that the radiation with acceptable toxicity should be given to the bone marrow and spleen. Subsequently RIT with ^{131}I -anti-CD45 has been added to the conditioning regimen with busulfan (Bu) plus Cy (BuCy) in the patients with the first CR AML [34]. Three-year non-relapse mortality and disease-free survival in this study was calculated at 21% and 61%, respectively. They have reported that the results were comparable by the International Bone Marrow Transplantation Registry (IBMTR) data using only BuCy in allogeneic HSCT. Similarly Pagel *et al.* added the RIT to the RIC regimens in elderly patients with advanced stage or high risk AML and showed the reliability of RIT in a phase I study [35]. Same researches used the ^{131}I -anti CD45 targeted radiotherapy in combination with Fludarabine plus 2 Gy TBI in younger patients (age 16 to 50 years) with advanced AML or high-risk MDS who underwent allogeneic HSCT [36]. They aimed to define the maximum tolerated dose (MTD) of radiola-

beled anti-CD45 antibody in addition to non-myeloablative conditioning regimes and to create better antitumor control with minimal toxicity in comparison with standard myeloablative regimens. Their study suggested that a maximum dose of 28 Gy could be delivered to the liver and the arbitrary limit of 43 Gy to the marrow might be unnecessarily conservative. Conjugation of anti-CD45 antibody with alternative radioisotopes including ^{90}Y is currently explored in clinical trials.

Another attempt in the studies was the use of anti-CD66 moAbs in leukemic patients. But leukemic blasts do not express CD66. Therefore, the anti-leukemic effect of CD66 RIT depends on “crossfire” from the beta-particles emitted by ^{188}Re . ^{188}Re -labeled anti-CD66 moAbs were used as a part of the standard myeloablative conditioning regimen including total body irradiation (12 Gy) ($n = 30$) or busulfan ($n = 27$) and high-dose cyclophosphamide +/- thiotepa prior to allogeneic or autologous HSCT in 57 patients with high-risk AML or MDS [37]. In median 26 months follow-ups, disease-free survival were 64% for 44 patients in the first or second CR or in very good partial remission (less than 15% blasts in the marrow at transplantation) and only 8% for those with more than 15% blasts in the marrow at transplantation. Likewise, targeted marrow irradiation with ^{188}Re -anti-CD66 moAbs were used in 20 patients with Philadelphia chromosome-positive acute lymphoblastic leukemia or advanced CML prior to allogeneic HSCT [38]. With a median follow-up of 54 months (range 23–81) overall and disease-free survival were 29% (95%-CI 14–58) and 25% (95%-CI 12–53), respectively. Subsequently, conjugation of anti-CD66 with ^{188}Re or ^{90}Y were added to a reduced intensity conditioning regimen in 20 patients with a median age of 63 years (range: 55–65 years) suffering from acute leukemia ($n=17$) or MDS ($n=3$) [39]. The probability of survival was estimated as 70% at 1 year and 52% at 2 years post-transplant. They concluded that ^{90}Y -anti-CD66 moAbs were more feasible and less nephrotoxic than ^{188}Re .

Briefly, the use of RIT is an attractive approach to increase conditioning prior to HSCT. The randomized studies in refractory aggressive or indolent NHL show the superiority of adding RIT. Nevertheless, the addition of standard dose RIT to the conditioning regimen in autologous transplantation is a valuable research topic. In allogeneic transplantation, until displaying the superiority of RIT-based conditioning regimen in controlled randomized studies, this approach should only be considered within clinical trials.

4. Alemtuzumab (Campath)

Alemtuzumab is a human originated MoAbs to CD52 that normally expresses on B and T lymphocytes, macrophages, monocytes, natural killer cells, and some dendritic cells. While alemtuzumab efficiently reduces both T and B cells from the circulating blood, it has minimal or no effect on hematopoietic progenitor cells [40].

Anti-CD52 is often used in the treatment of chronic lymphocytic leukemia. But adding CD52 to the conditioning regimens in allogeneic HSCTs in many malign hematological diseases has reduced the frequency and severity of GvHD as well as decreased the risk of graft rejection [41-43]. Also alemtuzumab in combination with fludarabine and Cy in allogeneic HSCT for

acquired aplastic anemia was associated with a very low incidence of chronic GvHD and excellent survival [44-49]. However, the studies have reported that alemtuzumab led to increase the frequency of opportunistic infection, in particular Cytomegalovirus, Epstein-Barr virus, and Adenovirus, and the risk for the recurrence of the underlying disease due to the reduction of graft versus tumor effects.

5. Gemtuzumab Ozogamisin

Gemtuzumab ozogamisin (GO) is a mAb to CD33 conjugated with human calicheamicins. It has been withdrawn from the market by the US Food and Drug Administration in 2010 because of the increasing risk of liver sinusoidal obstruction, and a lack of data for the efficacy and safety. Recently many studies have been published about the use of GO in the treatment of CD33+ AML patients as a part of induction therapy or consolidation [50-51]. Furthermore, phase I/II studies have reported that the use of GO as a part of MA or RI conditioning regimens in allo-HSCT setting could be safe and efficient in poor-risk AML patients [52-54]. In addition, a pilot study has been recently published about the administration of GO combined with azacytidine as the maintenance treatment of post-transplant relapses in AML [55].

6. Conclusion

Although many studies have been published for the additions of MoAbs to the conditioning regimens for HSCTs, there are no sufficient data to determine the optimal dose and administration schedule of the MoAbs until now. However, rituximab recently has been widely used in many single-arm studies in NHL patients who underwent allogeneic HSCT. Another controversial issue is about the use of RITs. Randomized data do not support incorporating RITs into the conditioning regimens for either autologous or allogeneic SCT settings. The high-dose RITs should be used in refractory or advanced malign hematological disease in specialized centers though lacking randomized data. The standard-dose RIT is also a good research topic for lymphoid malignancies planning high dose therapy with autologous rescue or allogeneic SCT.

Moreover, given the reduced risk of graft failure and GvHD with alemtuzumab but increased risk of disease relapse and the incidence of opportunistic infections, the use of alemtuzumab in the allogeneic SCT should be considered in patients with matched unrelated or mismatched related donors. Owing to the shortage of studies on GO, another MoAb, with the reuse, GO should be used in clinical trials.

In conclusion, it is anticipated that additional MoAbs to the conditioning regimens will be routinely used in the next door following by the proven clinical efficacy and safety.

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