Bone Marrow Transplantation (2019) 54:26–34
https://doi.org/10.1038/s41409-018-0227-0

REVIEW ARTICLE

Prevention and treatment of relapse after stem cell transplantation by cellular therapies

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Received: 20 October 2017 / Revised: 28 March 2018 / Accepted: 4 April 2018 / Published online: 24 May 2018

Abstract

Despite recent advances in reducing therapy-related mortality after allogeneic stem cell transplantation (alloSCT) relapse remains the major cause of treatment failure and little progress has been achieved in the last decades. At the 3rd International Workshop on Biology, Prevention, and Treatment of Relapse held in Hamburg/Germany in November 2016 international experts presented and discussed recent developments in the field. Here, the potential of cellular therapies including unspecific and specific T cells, genetically modified T cells, CAR-T cells, NK-cells, and second allografting in prevention and treatment of relapse after alloSCT are summarized.

Unmodified and tumor specific donor T cell responses after allogeneic stem cell transplantation

Alloreactive donor derived T-cell responses are crucial mediators of the therapeutic effect of alloSCT which is based on recognition by donor T cells of polymorphic genetic differences between donor and recipient [1, 2]. This T cell reactivity is fundamentally not different from recognition of virally infected cells being the recognition of viral (nonself) peptides presented in the context of HLA molecules expressed on the infected cells. The immune response is usually initiated by the presentation of peptides derived from viral proteins in HLA class I and or HLA class II molecules on dendritic cells (DC) when they are activated by danger signals. During thymic selection, T cells are deleted that are capable of recognizing autologous antigens in the context of self HLA molecules [3], resulting in a repertoire consisting of T cells that are capable of recognizing any composition of peptides presented in HLA molecules that are different from self-peptide/self-HLA combinations [4].

As 2–10% of the peptidome presented on the cell surface consists of polymorphic peptides even following HLA-identical transplantation a large number of potential nonself antigens can be presented by recipient cells to provoke an immune response by donor T cells [5]. Alloreactive T cells recognizing polymorphic antigens expressed on the hematopoietic system from the recipient including the

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malignancy will cause the specific graft versus leukemia (GVL) reactivity. If donor T cells recognize non-hematopoietic cells, graft-versus-host disease (GVHD) will occur which dominantly targets tissues containing high frequencies of professional antigen presenting cells like DC [1, 2, 6]. DC are derived from the hematopoietic system and therefore are likely to highly express multiple antigens that are co-expressed on other hematopoietic cells, especially cells of myeloid origin. This may be one of the reasons why an allo immune response provoked after alloSCT is likely to exert reactivity against patient hematopoietic cells including the malignancy if the DC are of recipient origin. If the immune response against DC is provoked in inflamed tissue where the DC will pick up antigens from the damaged organ, it is likely that an immune response will occur targeting also non-hematopoietic target tissues resulting in GVHD [7].

The most simple way to provoke a relatively specific GVL reactivity after alloSCT may be to administer T cells by donor lymphocyte infusion (DLI) under circumstances when there is no or limited tissue damage, when recipient derived DC's are not loaded with high frequencies of antigens derived from these tissues [8]. This may be achieved when first alloSCT is performed under circumstances where donor T cells are depleted from the graft or after in vivo T-cell depletion using antibodies or cyclophosphamide early after transplantation [9–11]. Subsequently, donor T cells can then be administered when tissue damage is restored, viral infections are limited, and part of the professional DC's of recipient origin is replaced by donor DC's [8, 12]. This may allow the induction of a T cell response of limited diversity and magnitude specifically targeting the hematopoietic system of the recipient [13]. Obviously, the immune response should be diverse enough to target at least multiple antigens, since otherwise antigen negative variants can easily escape the T cell response. Only a polyclonal T cell response targeting several antigens is likely to be highly effective in eliminating the (malignant) hematopoietic cells of recipient origin. Thus, timing and dosing of unmodified DLI is probably the most simple and effective way to separate GVL from GVHD reactivity.

Alternatively, attempts can be made to only target polymorphic antigens expressed on hematopoietic cells of recipient origin. This may be achieved by gene transfer into donor T cells of T cell receptors(TCR) specific for peptide/HLA complexes only expressed on hematopoietic cells of recipient origin like the HA-1 antigen expressed in the context of HLA-A2 [14], or by inducing in vitro or in vivo T-cell responses against polymorphic antigens specifically expressed on hematopoietic cells [15–19]. Although these approaches appear to be attractive, they are logistically complex and not easily broadly applicable. At this stage, only a few clinical studies with limited positive results have been published. Improved technologies are necessary to make this an efficiently applicable strategy.

Genetically modified T cells

The importance of T-cells for cancer treatment has been initially recognized by the observation that their infiltration at the tumor sites correlates with a good prognosis [20].

Nowadays, the potential of T-cell immunotherapy to fight cancer has been widely demonstrated by the graft-versus-leukemia (GvL) effect observed after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Unfortunately, the paucity of T cells specific for tumor antigens and the risk of inducing life-threatening graft-versus-host disease (GvHD), are still limiting the therapeutic window of allogeneic hematopoietic cell transplantation and donor lymphocyte infusion (DLI). Recent technological advancements have provided new tools to generate engineered T cells potentially able to overcome these limitations. Cell therapy with genetically engineered lymphocytes is indeed becoming a new promising therapeutic modality [21]. In the context of allo-HSCT, to improve the safety profile of DLI and to separate the beneficial effect of GvL from GvHD, one of the most attractive possibility is to genetically engineer T-cells with a suicide gene or to redirect their specificity against tumor antigens with chimeric antigen receptor (CAR) and T cell receptor (TCR) gene therapy [22–26].

After >20 years of preclinical and clinical studies [27–30] suicide gene therapy has currently reached conditional approval in Europe, in the context of haploidentical stem cell transplantation, thus opening the road for many new advanced T cell therapy products. Among these CAR-T cells have probably produced the most impressive clinical results in B-cell malignancies in recent years: [31–35]. Compared to CARs, TCR-based therapy has the advantage of targeting also intracellular tumor antigens. In addition, the physiologic TCR signaling promotes T cell survival, leading not only to the generation of anti-tumor effectors, but also to long-term immunological memory, able to prevent tumor relapse.

Despite its potential, suboptimal therapeutic effects have been registered [25] possibly due to the mutual competition for cell surface expression of the transgenic tumor-specific TCR with the endogenous one and to the mispairing of endogenous and exogenous TCR chains in a single T-cells. Newly generated hybrid receptors observed in mice [36]; and in vitro with human cells [37], harbour unpredictable and potentially harmful specificity, thus raising safety concerns. To address these hurdles, several strategies have been described aiming at promoting preferential assembly/surface expression of the exogenous α and β TCR chains

[38, 39]. To completely and permanently abolish the expression of the endogenous TCR repertoire and fully redirect T-cell specificity, the TCR complete gene editing strategy has been developed, based on the targeted disruption of the endogenous TCR αβ loci with zinc-finger nucleases followed by transduction of T-cells with lentiviral vectors carrying high-avidity anti-tumor TCRs [40]. As this method involves multiple manipulation steps and generates small number of redirected T-cells, a simplified TCR gene single editing (SE) protocol was established, based on the disruption of the solely TCR α chain followed by the simultaneous introduction of the tumor-specific TCR chain genes [41]. Edited T-cells showed a high killing activity against tumors and a higher specificity profile than cells redirected with conventional TCR gene transfer in vitro and in vivo, thus demonstrating that the editing procedure generates tumor-specific lymphocytes with improved safety and efficacy profile. Notably, the SE protocol ensures the production of high numbers of extremely fit tumor specific T-cells in 2–3 weeks, improving the feasibility of its clinical translation. The more recent development of the CRISPR/Cas9 system, allowing the simultaneous editing of more than one gene by multiple sgRNAs, has represented a further step forward in the field, enabling the simultaneous disruption of both TCR chains and a consistent shortening of the protocol used for the generation of TCR edited cells. Recently, the TCR disruption approach has been coupled to CAR gene transfer, and successfully tested in 2 pediatric patients affected by B-cell malignancies [42]. The TCR genome editing approach can be also exploited to foster targeted integration of a transgene, such as a tumor-specific CAR, into the TCR locus, thus permitting to redirect T cell specificity in a single genetic manipulation step [43].

However, broad range exploitation of adoptive T cell therapy needs to address different functional challenges represented by the immunosuppressive microenvironment [44] and by chronic TCR signaling which may lead to an exhausted phenotype with upregulation of inhibitory receptors [45]. To overcome these limitations the infusion of tumor-reactive T cells can be combined with alternative approaches, such as for example, checkpoint inhibitors. Alternatively, T cells might be further engineered to disrupt genes involved in T cell inhibition [46, 47] and/or to provide immunoenhancing molecules and immunostimulatory cytokines [48, 49]. Furthermore, the choice of the tumor antigen and the identification of the optimal T-cell subset for effective immunotherapy deserve some further consideration. To overcome the selection of tumor variants characterized by antigen loss upon therapy, multiple tumor antigens should be targeted, avoiding off-tumor effects while retaining on-tumor benefits. Concerning the optimal T cell subset to be used in immunotherapy studies recent evidences obtained from clinical gene therapy trials [30, 50] and from in vivo studies candidate two novel populations of T lymphocytes, such as memory stem T cell (Tscm) [51] and Th17 CD4 T cells [52] as promising weapons for T cell therapy, ensuring optimal functional anti-tumor profile, and long-term persistence. The successful wide exploitation of T cell therapy will require efforts for a sustainable manufacturing procedure in order to offer a precise and personalized therapeutic approach to all cancer patients in need.

Chimeric antigen receptors (CARs) are synthetic molecules that combine an antigen recognition domain of an antibody with intracellular T cell signaling domains into one single chimeric protein. Through gene transfer techniques, the T cell can be genetically altered to stably express the CAR on the cell surface, conferring novel antigen specificity [53]. The best studied and most successful CARs have been used to target CD19 on B cell malignancies. Overall and complete response (CR) rates for patients with relapsed and refractory CLL are significant at just over 50% and 28%, respectively [34], with responses even higher in some studies [32, 54, 55]. Response rates for patients with relapsed and refractory B-cell ALL are even more impressive with up to 90% of patients consistently achieving CR [31, 56, 57]. While allogeneic transplant has been the only curative therapy for relapsed ALL, transplant is largely ineffective with active disease and is often considered inappropriate due in part to the very high relapse rates. As a "bridge to transplant", CAR T cells will induce CR in 90% of patients, allowing many to undergo potentially curative allogeneic SCT [57, 58].

CAR T cells are a major advance for both the prevention and treatment of relapse after transplant. A number of patients with relapsed CLL and NHL received CAR T cells from their original donor with limited GVHD and potent anti-tumor activity even in cases where standard DLI had failed [59]. Most patients treated for relapse after allogeneic SCT have had ALL and are infused with autologous CAR T cells, though in most cases, those cells are donor in origin. Remission rates of ~90% have been consistent [32, 60], this is in comparison to the 0–20% often transient CR rate anticipated from standard DLI. Importantly, no GVHD has been reported in this setting.

While CAR T cells will likely have an important role as a bridge before and as treatment after transplant (both situations where there are few if any other effective therapies), the more difficult consideration will be whether or not they can be applied instead of transplant. Several reports suggest that at least for some patients, CAR T cells will indeed induce long-term remissions without subsequent allogeneic SCT. In CLL, some of the first patients treated remain in remission >6 years from infusion [61, 62] (and unpublished data). The first pediatric patient to be treated with CAR T cells at Children's Hospital of Philadelphia (CHOP) for refractory ALL remains in remission 5 years later with no

subsequent therapy [63] (and S. Grupp, personal communication). In one large cohort, EFS was 45% at 1 year [64], relapses beyond one year are very unusual and most patients did not go on to subsequent allogeneic SCT. In one retrospective comparison, survival was not different after CAR T cell therapy for ALL in patients who achieved CR and who did or did not go on to subsequent transplant [65]. It is very likely that at least for some patients, CAR T cell therapy may be able to replace allogeneic SCT. How to identify these patients remains to be determined, but this group may include patients with persisting CAR T cells, prolonged B cell aplasia, or MRD-negative responses.

CAR T cell therapy results in a number of unique toxicities. Since CD19 is expressed on normal B cells, a consistent side effect is B-cell aplasia and hypogammaglobulinemia. This is often managed with intravenous immunoglobulin replacement. The most unique and serious toxicity has been cytokine release syndrome (CRS) [66]. IL-6 seems to be the key regulator with levels dramatically elevated in almost every patient with CRS [67]. Tocilizumab, an IL 6 receptor antagonist, has been used successfully in many cases to rapidly reverse symptoms associated with severe CRS [63, 67]. CAR T cells are also associated with a number of neurologic toxicities [66]. They do not respond immediately to anti-IL-6 therapy. In addition, a number of cases of lethal cerebral edema have been reported after CAR cells. However, neurologic toxicity may be more frequent with some CAR constructs than others, highlighting that not all CAR T cells have the same toxicity profile. Overall, toxicity has been manageable in most cases.

With a 90% CR rate for patients with relapsed, refractory ALL, CARs have been a very successful "bridge to transplant", and have been dramatically more effective than DLI (or any other therapy) for relapse after transplant. More intriguing is the possibility that CAR T cells will not only prevent and effectively treat relapse, but may have the potential to eliminate the need for transplant in some patients.

Natural killer cells (NK-cells)

Natural killer (NK) cells were discovered based on their ability to kill target cells without prior sensitization. HLA class I-recognizing inhibitory receptors are responsible for both inhibition and the acquisition function, a process called NK cell licensing or education. The key to exploiting NK cells for therapy is to overcome inhibitory signals, promote activation and to avoid tumor induced immune suppression.

Recent studies have focused on allogeneic NK cells to treat advanced AML. We pioneered a lymphodepleting regimen with high dose cyclophosphamide and fludarabine followed by infusion of HLA-haploidentical NK cells from related donors [68]. IL-2 was administered with the intent of further expanding NK cells in vivo. We have treated over 50 patients with this regimen, some with the addition of IL-2 diphtheria toxin to deplete IL-2 receptor ($CD25^{hi}$) expressing regulatory T cells (Treg) [69]. Response rates across protocols continue to be in the 30–50% range. These outcomes suggest that the NK cells themselves play a role in the antileukemia response over and above the activity of the chemotherapy preparative regimen. Patients achieving remission also had a significantly higher proportion of circulating donor NK cells, further suggesting that persistence and expansion correlates with clinical efficacy. Limitations of NK cell therapy include the need for (1) better activation without inducing exhaustion or other suppressive mechanisms, (2) functional memory, and (3) better specificity. Another limitation of NK cell therapy is the number of cells available from a donor apheresis product. To overcome this limitation, promising strategies are proposed to ex vivo expand NK cells using K562 feeders transduced with 41BB-ligand and either membrane bound IL-15 [70] or IL-21 [71, 72]. This later strategy with IL-21 feeders has been translated clinically and a promising phase 1 clinical trial has recently been published [73].

IL-15 is the homeostatic receptor controlling NK cell development, proliferation, and activation. Recombinant human IL-15 (rhIL-15) is a cytokine and growth factor capable of expanding and activating T cells and NK cells. Based on preclinical, non-human primate and clinical trial data at the NCI [74], we tested systemic administration of rhIL-15 by daily intravenous or subcutaneous dosing in our adoptive NK cell schema. We have established the clinical MTD of rhIL-15 when used to promote NK cell adoptive transfer. As an alternative approach, a novel IL-15/IL-15Rα-Fc construct, ALT-803 (Altor Biosciences), was designed to physiologically trans-present IL-15 and prolong its serum half-life allowing for intermittent weekly dosing. A first-in-human phase 1 trial of ALT-803 in patients who relapsed after alloHCT is complete and the next step is to test ALT-803 after HCT to prevent relapse.

Resent discoveries show that NK cells can have properties of immune memory. Cytomegalovirus (CMV) infection is uniquely associated with expansion of $CD57^{+}$ NK cells expressing the activating receptor NKG2C [75]. We have reported that in vivo expanded of $CD57^{+}NKG2C^{+}$ NK cells (referred to as adaptive NK cells) persist for over one year and are associated with reduced leukemia relapse after reduced intensity HCT [76]. Ex vivo expansion to enrich for adaptive NK cells represents a new strategy to obtain high numbers of highly functional NK cells to treat cancer patients. We have developed an NK cell product using a gylcogen synthase kinase 3 inhibitor that drives

maturation of NK cells and enhances their functional activity, which is currently in clinical trials [77].

The Fc receptor CD16 is present on most peripheral blood NK. Upon recognition of antibody-coated tumor cells, CD16 delivers potent activating signals to NK cells, leading to target elimination through direct killing and cytokine production. In addition to monoclonal antibodies, we have focused on a platform using bispecific killer engagers (BiKEs) constructed with a single-chain Fv against CD16 and a single-chain Fv (scFv) against a tumor-associated antigen. We initially developed a CD16x33 BiKE to target myeloid malignancies (AML and myelodysplastic syndrome) [78]. One of the most remarkable properties of this drug is its potent signaling. However, the BiKE does not sustain NK cell survival or deliver a proliferative signal to NK cells. Therefore, we have added a third function to our BiKE by inserting IL-15 between the two scFv components. Our trispecific hybrid drug (CD16xIL15xCD33 TriKE) binds NK cells, myeloid CD33 +targets and generates an IL-15 proliferative and survival response [79]. Immune engagers are not the only way to make NK cells antigen specific. Some have proposed that genetic modification of NK cells may be superior "CAR" drivers [80, 81]. A clinical trial using cord blood derived NK cells and CD19 CAR has been initiated (MD Anderson) and will serve as proof-of-concept for his approach.

Second allogeneic stem cell transplantation to treat relapse after allo-SCT

Allogeneic stem cell transplantation (allo-SCT) is the only curative therapy for many patients with a hematologic malignancy. However relapse remains the leading cause of treatment failure and optimal treatment for relapse after allo-SCT is still poorly defined. Limited therapeutic options are generally available for these patients and they usually face a very poor prognosis [82, 83]. However, a second alloSCT is probably the best therapeutic option for long term survival.

Historically, re-transplantation with a second myeloablative conditioning regimen was limited by a very high rate of non-relapse mortality, up to 46% [84–86]. Subsequently, the development of reduced intensity conditioning (RIC) regimens allowed for a significant decrease of the toxicity of a second allo-SCT. The largest study investigating the use of a RIC allo-SCT after an initial myeloablative conditioning regimen (MAC) allo-SCT reported an NRM rate of 24% at one year [87]. Similar NRM rates have been reported in others studies [88–90]. More recently, the EBMT evaluated the use of a second RIC allo-SCT after an initial RIC allo-SCT in 243 adult patients with acute leukemia [91]. This strategy was associated with an NRM rate of 22% at 2 years. Overall, a second allo-SCT to treat relapse after an initial allo-SCT appear to be an acceptable option provided a RIC regimen is used.

Time of relapse after first and disease status at time of second transplant were shown to be the most important predictor factors for long survival after a second allo-SCT. Indeed, the worse prognosis of an early relapse after allo-SCT is well documented in the literature. For instance, Levine et al. [92]. reported that acute myeloid leukemia (AML) patients who relapsed 6 months or later after allo-SCT were almost four times more likely to achieve remission compared to those who relapsed in the first 6 months after allo-SCT. The duration of remission following the first transplant procedure is clearly a major factor that can impact the outcome of patients after a second allo-SCT as described in different series [85, 87, 90, 93]. Vrhovac et al. [91] reported a significantly worsened overall survival (OS) in patients that relapse within the first 225 days after allo-SCT compared to patients that relapse latter (10% versus 36%, $p < 0.001$). Furthermore, patients not in complete remission at time of second transplant had significantly inferior outcome with an OS of 16% compared to 41% in patients in CR ($p < 0.001$) [91]. Also, the importance chemosensitivity of the disease has been consistently reported in the different studies [93, 94].

The choice of the donor for a second allo-SCT is another matter of debate. Christopeit et al. [89] evaluated the relevance to select a new donor for a second allo-SCT, which was done in 54.2% of these patients. No improvement in OS was reported in patients who received a second transplant from a new donor compared to patients who received a second allo-SCT from the same donor. However, only matched related or unrelated donors were used in this study. The use of haploidentical donors may change the situation; [95] because HLA disparity may enhance the graft versus leukemia effect and improve disease control. Furthermore, haploidentical donors are quickly available, allowing to perform transplant immediately once patients achieve CR. Therefore, the use of haploidentical donors appears to be a promising option for a second allo-SCT.

Overall second allo-SCT to treat relapse after a first allo-SCT is a feasible approach, in particular in patients who relapse at least 6 months after the first allo-SCT and with a good disease control at time of the second allo-SCT. A MAC regimen is likely to be avoided in this setting to decrease the NRM rate and improve outcome. While the use of the same donor is feasible, a change of donor change may become a preferred choice with the advent of haploidentical allo-SCT strategies.

Cellular therapies with unmanipulated T cells (DLI) or with hematopoietic stem cells in the context of a second allograft have been used for many years as salvage option for relapse after stem cell transplantation, but its inherent complication such as graft versus host disease limited its

broader application. New selection procedures and technologies for genetic manipulation of adaptive and innate immune cells has opened new possibilities for more tumorspecific and hopefully less toxic relapse prevention and treatment options.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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