Acta Haematologica Polonica 2024
Number 2, Volume 55, pages 90–96
DOI: 10.5603/ahp.98148
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

VIA MEDICA

Treatment of resistant viral infections after allogeneic hematopoietic stem cell transplantation using virus-specific T cells

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely used in the treatment of malignant and non-malignant diseases. Patients treated with allo-HSCT receive immunosuppression, which lowers the organism's immune response. This leaves a significant period during which the host is seriously deficient in T cell immunity. Viral infections are therefore one of the major causes of morbidity and mortality in these patients. Available prophylactic and preventive antiviral pharmacotherapies are often insufficient or limited due to toxicity, ineffectiveness, or the development of drug resistance, and additionally do not provide long-term protection or immunological memory.

A current extension of virostatic agents is the transplantation of antiviral immunity through adoptive transfer of virus-specific T cells (VSTs) against ADV, CMV, or EBV. Antigen-specific adoptive immunotherapy holds promise in selectively targeting and eradicating host cells by identifying particular antigens, such as those associated with specific viral infections and cancers. The successful application of adoptive transfer of antigen-specific effector immune cells has been demonstrated in the treatment of opportunistic viral infections following HSCT. VSTs exhibit significant potential as a valuable addition to current treatments for viral reactivation and disease, showing robust and enduring response rates with a manageable side effect profile.

Keywords: cell therapy, allogeneic stem cell transplantation, viral infections, lymphocytes T, virus-specific T cells

Acta Haematologica Polonica 2024; 55, 2: 90–96

Introduction

Hematopoietic stem cell transplantation (HSCT) is an important strategy for the treatment of malignant diseases (mainly leukemias and lymphomas) and non-malignant diseases (primary immunodeficiencies, metabolic diseases). However, achieving the desired outcome can be hampered by a wide range of transplant-related complications, including viral infections, which are a leading cause of morbidity and mortality in transplant patients [1].

There are many factors influencing the risk of infectious complications after HSCT and factors related to impaired reconstitution of the immune system after treatment. In the classical approach, the most important are neutropenia occurring immediately after the preparatory treatment (conditioning), functional and quantitative cellular disorders, as well as humoral disorders of the immune system related to delayed immune reconstitution during treatment, and graft-versus-host disease (GvHD) in recipients after allo-HSCT or in the course of other

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Received: 07.11.2023 **Accepted:** 08.01.2024 **Early publication:** 25.03.2024

immunological complications occurring after transplantation [2, 3].

About one third of deaths caused by infections are caused by viruses, mainly human cytomegalovirus (CMV), Epstein-Barr virus (EBV) or human adenovirus (AdV) [4, 5]. After HSCT, the latent virus may reactivate and manifest itself as post-transplant lymphoproliferative disease (PTLD) [6, 7]. Frequently, local reactivations tend to resolve on their own, whereas systemic infections, particularly when a risk factor weakens T-cell protection, lead to significant morbidity and mortality [5, 8].

Despite the fact that pharmacological therapies are available for the treatment of viral infections, many of them are, unfortunately, ineffective. This is sometimes due to drug resistance and sometimes to the need to withhold treatment due to drug-related toxicity. Furthermore, long-term treatment is expensive.

For all of these reasons, virus-specific T cells (VSTs), which are mainly cytotoxic T lymphocytes (CTLs), are increasingly being explored as a treatment option for refractory viral infections in transplant patients [1].

Complications after allo-HSCT and conventional treatment

Bacterial infections occur with a similar frequency after allo-HSCT and auto-HSCT transplantation, while fungal and viral infections occur much more often after allo-HSCT, which is due to the possibility of profound immunological disorders after allo-HSCT, related to HLA incompatibilities between the donor and recipient, the immunosuppressive therapy used, and the possible presence of GvHD [9].

CIBMTR (Center for International Blood and Marrow Transplant Research) registry data shows that among the causes of HSCT failure, infections account for 12% of deaths after HSCT from matched family donors, for 17% of deaths after HSCT from unrelated donors, and for 8% of deaths after auto-HSCT. American data shows that infections after allo-HSCT occur in 82% of children, but in only 21% of children with solid tumors and lymphomas after auto-HSCT, and in 49% of children with acute leukemias, again after auto-HSCT [9–11].

As a result, patients after allo-HSCT often experience reactivation of latent viruses, mainly herpes viruses, most often CMV and EBV, which constitute a significant clinical problem after allo-HSCT requiring the use of pre-emptive or targeted therapy. There is also frequent infection and reactivation of the BKV polyoma virus, which causes the development of hemorrhagic cystitis.

The clinical picture of latent virus infections is related to their direct effect, causing the development of a disease typical for a given virus (i.e. most often with CMV — pneumonia, liver, brain, gastrointestinal tract, and bone marrow failure; with EBV — PTLD, and lymphoproliferative syndrome; with VZV — herpes zoster; and with HHV6 — encephalitis). There is also an indirect effect related to the negative impact on the immune system contributing to the development of subsequent infections, including other viruses and fungal infections.

Undoubtedly, antiviral treatment has a harmful effect on the immune system and the function of the regenerating bone marrow. A common complication of viral infection and antiviral treatment is secondary bone marrow failure, which affects the functioning of the entire body and has an unfavorable effect on the transplant procedure. In other words, viral infections can undermine the best efforts of the transplant center and the effect of hematopoietic cell transplantation and anticancer treatment [9].

CMV is defined as a beta herpes virus. In monocytes, CMV causes lifelong latency [12, 13]. Whether the CMV infections are acute or reactive, they can cause multisystem diseases (e.g. pneumonia, hepatitis and encephalitis). Antiviral drugs, including gancyclovir and foscarnet, or newer drugs such as maribavir, brincidofovir and letermovir, reduce the frequency of infections in transplant recipients. Unfortunately, they are expensive and often accompanied by toxicity and antiviral resistance [14–16]. For CMV IgG positive adult HSCT-recipients, letermovir is approved CMV prophylaxis. Acyclovir/valacyclovir is not sufficiently effective against CMV. Gancyclovir and foscarnet have been shown to be effective but toxic in HSCT recipients (Table I). Moreover, valgancyclovir is effective in solid organ transplantation but causes myelosuppression, and therefore its use is greatly limited in HSCT recipients [17].

In children, the situation differs but there is data available on its off-label use with positive impacts on allo-HCT outcomes due to its favorable safety profile and high efficacy in preventing CMV reactivation [18–20]. Preemptive therapy is considered the standard strategy for CMV prevention after allo-HSCT. Under this, patients are monitored weekly for CMV reactivation by PCR. Current recommendations for preventive therapy for allo-HSCT patients according to the European Conference on Infection in Leukemia include the use of letermovir which has grade AI (A = strongly recommended, I = based on a randomized trial) recommendations for CMV prophylaxis in adult allo-HCT recipients according to ECIL7, intravenous gancyclovir or foscarnet (first-line therapy), and valgancyclovir instead of intravenous gancyclovir or foscarnet (except for patients with severe GvHD of the gastrointestinal tract) [1, 17, 21]. The choice of drug has also been shown to depend on time after HSCT, risk of toxicity, and prior antiviral drug exposure.

EBV is known as a gamma herpes virus. EBV leads to B lymphocyte latency throughout life, and can cause fulminant infectious mononucleosis or lymphoproliferative disease in immunocompromised patients [22, 23]. The use of rituximab has reduced the incidence of PTLD. Unfortunately, the risk of primary immunodeficiency diseases (PID) in

Table I. Data on viral reactivation, viral disease, standard treatment and response rate in patients

Virus	Patients	Viremia [%]	Viral disease [%]	Treatment	Response rate [%]
AdV	Children	15–30	6–11	Cidofovir	60–80
	Adults	6–15	2	Brincidofovir	
CMV	Children	12–20	4	Gancyclovir	
	Adults	39	13	Foscarnet	70–80
				Valgancyclovir	
EBV	Children	11	1–7	Rituximab	60–70

AdV — human adenovirus; CMV — human cytomegalovirus; EBV — Epstein–Barr virus

patients still remains. Preventing EBV-PTLD mainly involves selecting a donor who is serologically compatible with the transplant recipient. The preventive use of antiviral drugs is not recommended for this indication. Individual studies have indicated the effectiveness of the anti-CD20 monoclonal antibody, rituximab, administered prophylactically after allo-HSCT in a group of patients with a high risk of developing PTLD. Currently, the most widely used drug in preemptive therapy is indeed rituximab, which prevents the development of full-blown PTLD in 89% of treated patients. The use of 1–2 doses of the drug is usually sufficient to reduce EBV viral load. This therapy is currently used in more than 80% of European transplant centers, which has significantly contributed to reducing the number of cases of confirmed PTLD [3].

Adenovirus is a non-enveloped DNA virus and is the main cause of respiratory and gastrointestinal diseases in immunocompromised patients. Cidofovir is active against adenoviruses, but its use is often limited due to its renal toxicity. In small studies, brincidofovir has demonstrated efficacy against adenoviruses and no significant renal toxicity, but has been associated with gastrointestinal toxicity [24, 25]. For preventive therapy of AdV infection, cidofovir is currently the recommended first-line drug. However, treatment outcomes are confounded by drug toxicity (Table I) [1].

BK virus is a polyomavirus associated with hemorrhagic cystitis and rare cases of pervasive multifocal leukoencephalopathy [26, 27]. Brincidovir is used for the prophylactic or preemptive treatment of BKV. Furthermore, it has been shown that second-generation ciprofloxacin (a fluoroquinolone) can prevent BK virus replication *in vitro* and lead to a reduction in BK virus spread after allo-HSCT [28].

Available prophylactic and preventive antiviral pharmacotherapies are often insufficient or limited by toxicity, ineffectiveness, and/or the development of drug resistance, and additionally they do not provide long-term protection or immunological memory [29]. T cell reconstitution is a key requirement for effective infection control after HSCT, given the central role of pathogen-specific T cells in infection surveillance. Therefore, strategies that accelerate pathogen-specific immunity and T cell regeneration may complement or replace available treatments [30].

Treatment of resistant viral infections after allo-HSCT

Conventional pharmacological products against viral infections have limited effectiveness and corresponding toxicity.

In 2022, the USA's FDA and the EU's EMA approved the medicinal product Ebvallo (tabelecleucel). This product is used for allogeneic T-cell immunotherapy specific for EBV, which targets and eliminates EBV-infected cells in an HLA (human leukocyte antigen)-restricted manner.

Another interesting method of treatment is an adoptive cell therapy of viral infections using infusions of VST, first suggested in 1990 [31]. Over more than three decades, hundreds of patients have been treated with lymphocytes with anti-viral activity, also referred to as CTL therapy [5].

Riddell and Greenberg administered only VSTs to their patient [31, 32]. They produced CMV-specific CD8+ T cells by *ex vivo* culture of the donor's PBMCs (peripheral blood mononuclear cells) in the presence of autologous CMV-infected fibroblasts. This was followed by clonal expansion and depletion of CD4+ T cells. They observed no significant side effects in any of the treated patients [31, 32].

Rooney et al. manufactured EBV-specific T cells for the treatment of PTLD by successively stimulating donor-derived PBMCs with irradiated autologous EBV-transformed B cell lines [5, 33, 34].

Interestingly, multiple VSTs have also been produced. The process was established by using direct isolation using a cytokine capture technique [35]. Khanna et al. presented a protocol in which multipathogen-specific T cells (expressing CD154) were isolated by magnetic cell separation [36]. The comparison of multi-VSTs isolated by CD137 expression or IFNγ production showed no significant differences in CD4+/CD8+ T cell functionality or frequency [37].

Clinical trials using CMV, EBV, and AdV-specific T cells for adoptive T cell transfer have demonstrated that T cell therapy is an attractive approach to restoring protective antiviral T cell immunity. Over nearly 30 years of adoptive T cell transfer, 74% of 246 patients responded to treatment, 85% responded to CMV-specific T-cell transfer, 62%

to EBV-specific T-cell transfer, and 74% to AdV-specific T-cell transfer. The dosage of VSTs depends on the risk of GvHD, the method of production, and the degree of HLA matching/mismatching. For *ex vivo* generated T cells, the recommended upper dose limit is 2.5×10^4/kg recipient CD3+ cell weight in HLA-mismatched/haploidentical donors, and 1×10^5/kg in HLA-matched donors [5].

The development of a manufacturing process for VST-cell products has overcome the difficulties associated with the transfer of adoptive T-cells. Nevertheless, regulatory obstacles, logistics, and the time-consuming selection techniques for producing VSTs, limit the broad application of this therapy. 'Off-the-shelf' VSTs are promising, but clinical efficacy has not yet been confirmed in placebo-controlled trials. Moreover, third-party T cells have demonstrated clinical benefits, but the explanation for *in vivo* persistence remains to be explored [38]. The phase III clinical trial TRACE (international and placebo-controlled) aims to create clinical data to enable adoptive transfer of VSTs to be incorporated into evidence-based treatment guidelines. It also aims to eventually make third-party T cells available as a standard treatment for refractory viral infections after HSCT [5].

Posoleucel (formerly known as ALVR105) is an off-the-shelf multi-VST product designed for administration to immunocompromised patients as a partially HLA-matched solution. It aims to treat or prevent viral infections or diseases caused by AdV, BKV, CMV and EBV. Posoleucel is designed to reinstate T cell immunity in patients experiencing a period of severe immune compromise between the conditioning and reconstitution phases of their immune systems. By acting as an immunological bridge, posoleucel has the potential to significantly decrease or prevent virus-associated morbidity and mortality, leading to notable improvements in patient outcomes. The transformative impact of posoleucel on the management of transplant patients was explored in a phase II open-label, proof-of-concept study involving 58 allogeneic HCT patients with treatment-refractory infections. In this study, 95% of patients treated with posoleucel exhibited a predefined clinical response, and the treatment was generally well-tolerated.

Additionally, a phase II multi-virus prevention trial showed that posoleucel resulted in a substantial reduction in the anticipated rate of clinically significant viral infections or diseases. By the week 14 primary endpoint, 88% of patients remained free of clinically significant infections caused by any of the six viruses targeted by posoleucel [39]. In their study, Pfeiffer et al. determined the feasibility and safety of posoleucel in allo-HCT recipients infected with one or more of these viruses. This open-label, single-arm trial, approved by the FDA and the Baylor College of Medicine institutional review board, included patients who had undergone allo-HSCT from any donor source starting from day 28 post-transplant [40].

An appealing feature of third-party off-the-shelf multi-VSTs is their swift availability, reducing potential delays in treating these often life-threatening viral infections. Out of 59 posoleucel VST lines, a suitable line was identified for 97% (58/60) of screened and eligible patients, allowing local patients to receive treatment within 48 hours. Clinical benefit was observed even when posoleucel was matched on a single HLA allele, although the majority of patients received lines matched at a median of two alleles. Posoleucel is derived from healthy, seropositive third-party donors rather than being sourced from autologous or HLA-matched HSCT donors.

The trial results indicate that posoleucel is a safe and effective therapy for severe viral infections following allogeneic HSCT. Its use could potentially reduce the morbidity and mortality associated with post-HSCT viral infections while avoiding the nephrotoxic and myelosuppressive side effects linked to conventional antiviral medications [40].

Adoptive T cell therapies targeting specific viruses are generally considered safe. However, in allogeneic products, there is a potential concern for GvHD, with reported incidences ranging from 5–16%, despite the viral specificity of the majority of cells [41]. Regardless of the cell source, occurrences of cytokine release syndrome and graft failure due to T cell-mediated inflammation are possible but have only been rarely reported [42, 43]. An unresolved issue revolves around the simultaneous use of immunosuppressive drugs, which can impact the expansion and function of infused T cells in the patient. Determining the optimal timing and composition of immunosuppression at the time of VST infusion remains an unanswered question [41].

VST production

VSTs are manufactured as patient-specific products, and the time required for procurement, production, and marketing approval testing precludes their use in acutely ill patients. Moreover, products must always comply with good manufacturing practices (GMP).

A possible solution to this limitation is the automated production of VSTs. Kim et al. and Kállay et al. [35, 44] have described a manufacturing process using an IFN-γ cytokine capture system (CCS) in a closed system. The process is based on the presentation of viral antigens on donor's lymphocytes. The presentation of the antigens is followed by magnetic separation of VST cells that responds to antigen stimulation with the expression of IFN-γ. The whole process uses a fully automated CliniMACS Prodigy® system from Miltenyi Biotec (Bergisch-Gladbach, Germany).

In terms of manageability, the VST manufacturing process using the IFN-γ CCS with CliniMACS Prodigy® is reliable. VST cells against one virus, and also multi-VSTs, can be manufactured in enough cell numbers for 100% of patients. The final cell product received from CliniMACS

Prodigy® is ready for infusion within two days. This shows a significant reduction in manufacturing time compared to *ex vivo* culture methods that took 2–12 weeks to complete [31, 45]. The fully automated CliniMACS Prodigy® system telescoped the time to completion to c.14 hours. This reduces infrastructure requirements and lightens the load on the GMP team. These manufacturing times are consistent with a study by Priesner et al. comparing CliniMACS Prodigy®-based manufacturing to CliniMACS Plus®-based manufacturing [46]. Using both methods to manufacture CMV-specific T cells from three healthy donors, they demonstrated that the recovery rate was comparable in both methods. However, the purity of the product was noticeably higher using CliniMACS Prodigy® (purity range on Prodigy® 79.2–96.4% vs. 19.2–81.1% on Plus®). A comparable preclinical study by Kim et al. extensively described the characteristics of five products of CMV-specific T cells from healthy donors' leukapheresis products [44].

Regarding the safety profile of VST treatment, no major safety concerns have been identified in previous studies evaluating the use of VST [31, 35, 47–50].

The production of VST cells, for each virus, is a time–consuming and expensive process. Therefore, intensive work is being carried out to establish protocols for producing multi-VSTs in a single step.

Conclusions

Despite the fact that some advances have been made in antiviral pharmacotherapy, the available products still show significant toxicity. Moreover, they are rarely able to control the virus without restoring T-cell immunity. New antiviral drugs (e.g. letermovir) have provided additional preventive measures, but the therapeutic options still remain limited. VSTs are promising in combating refractory viral infections in HSCT patients, whether it is treatment or prevention. Importantly, VST therapy has the potential to become a valuable clinical extension to the available treatments for viral infections, given its robust and durable response rates and tolerable side effect profile. In Poland, the decision is being taken to introduce VST therapy into the treatment of resistant viral infections in patients after allo-HSCT as part of a project financed by the Medical Research Agency (ALLOVISTA, project number 2020/ABM/01/00125).

Article information and declarations

Acknowledgements
Not applicable.

Authors contributions
Anna B — conceptualization, literature analysis, original draft preparation, review and editing; Alicja B, MB — literature analysis, original draft preparation, review and editing; KO, AŁ, RK — review and editing; KJ — conceptualization, review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interests
The authors declare no conflict of interests.

Funding
None.

Supplementary material
None.

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