Virus-specific T-cell therapy to treat infections in bone marrow transplant recipients

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Background

- Virus infection remains an appreciable cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT).

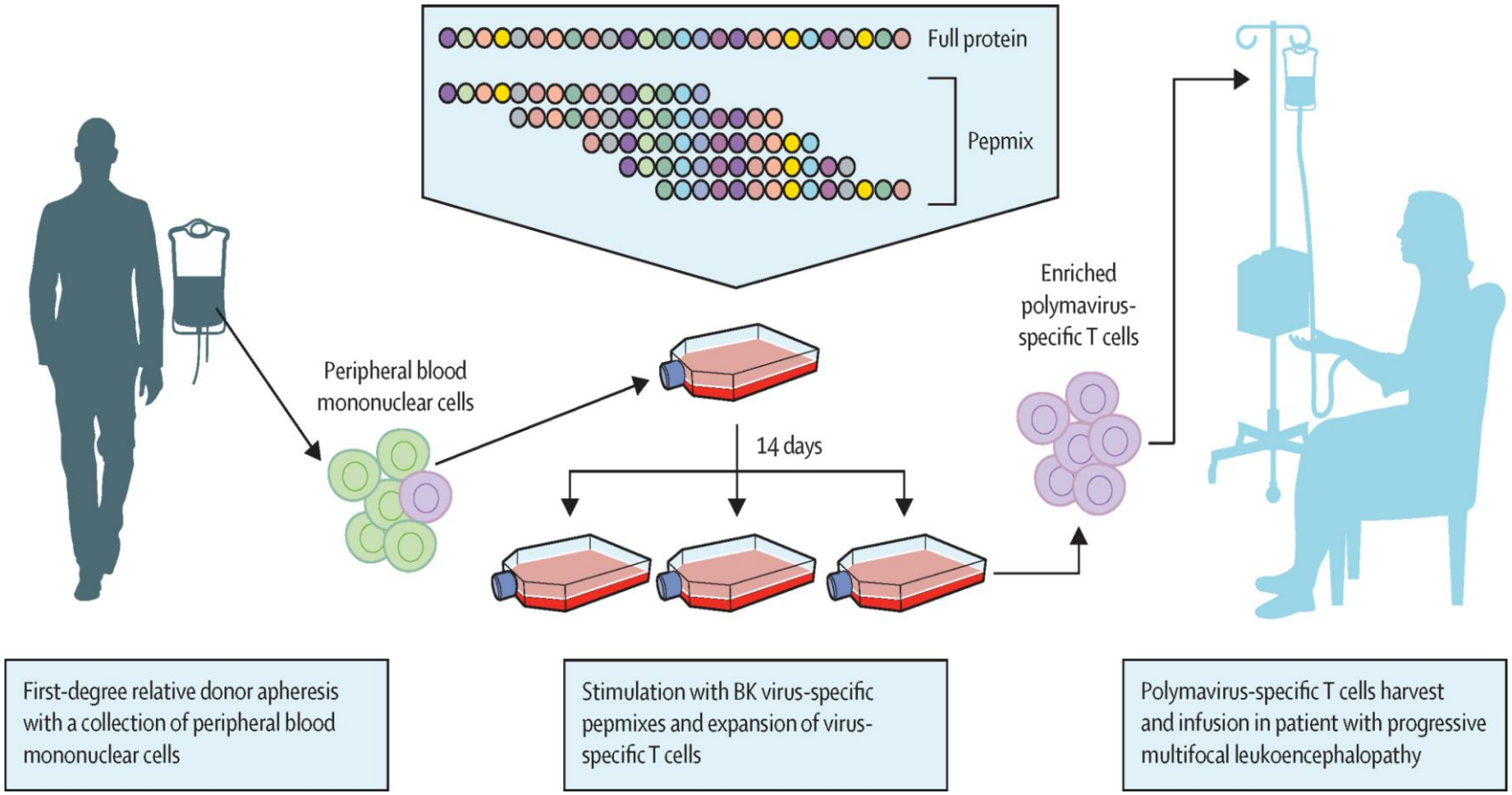
- Although pharmacotherapy may help prevent or treat viral disease, these drugs are expensive, toxic, and often ineffective due to primary or secondary resistance. Further, effective treatments are limited for many infections (e.g., adenovirus, BK virus), which are increasingly detected after transplantation.

- These deficiencies in conventional therapeutics have increased interest in an immunotherapeutic approach to viral disorders, leading to adoptive transfer of virus-specific cytotoxic T lymphocytes (VSTs), which can rapidly reconstitute antiviral immunity post-transplantation without causing graft-versus-host disease.

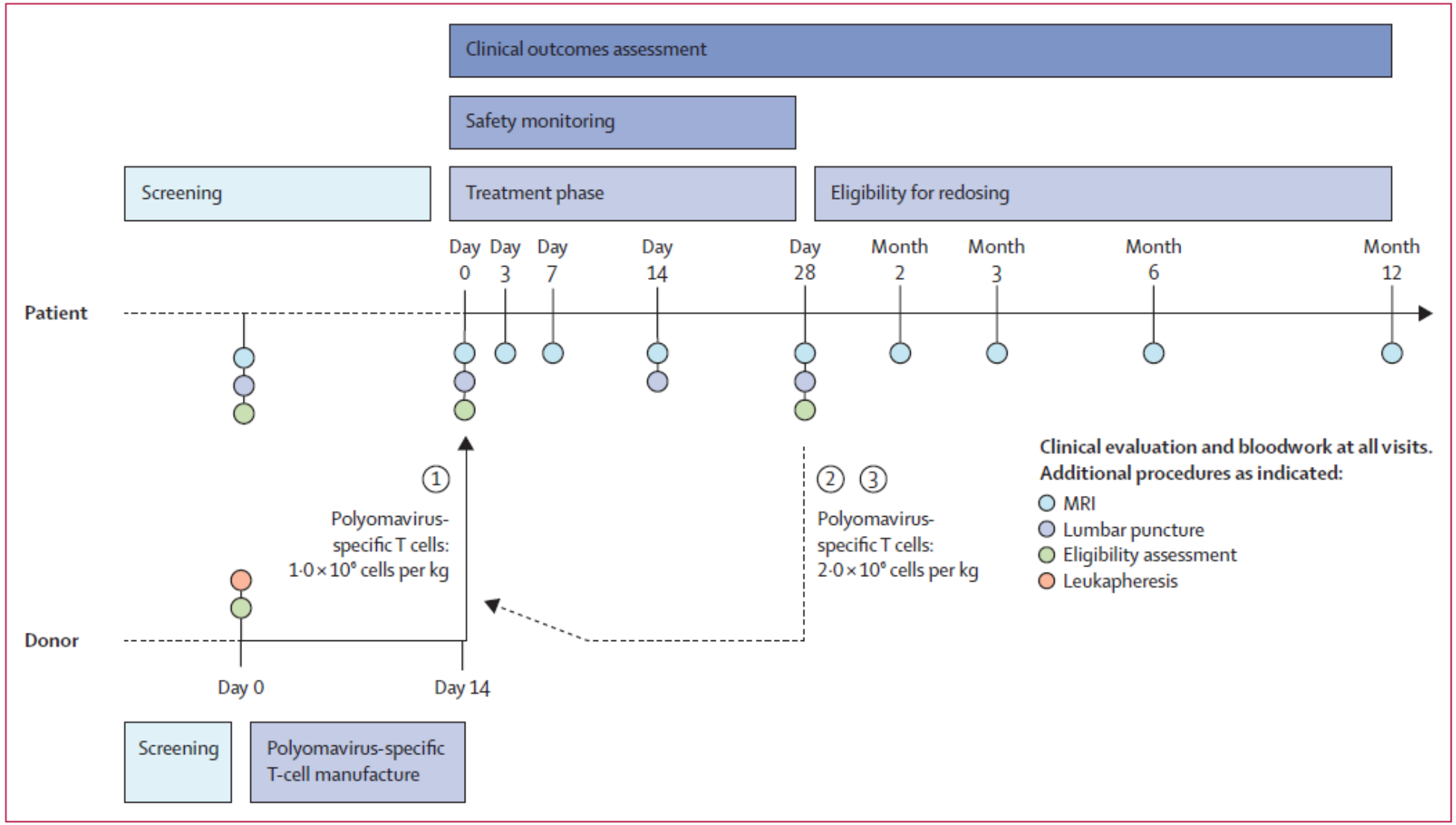
Generation time

- Historically, the process required a lengthy, 8- to 10-week culture period.

- In the process of optimization, which notably includes the use of gas-permeable culture flasks for rapid T cell expansion, the technique has become simpler and cheaper. Today, it is possible to generate VSTs from autologous antigen presenting cells pulsed with viral peptide libraries in less than 14 days.



BKV-specific T-cell manufacturing process



Findings Between April 7, 2016, and Oct 19, 2018, 26 patients were screened, of whom 12 were confirmed eligible and received treatment derived from 14 matched donors. All administered polyomavirus-specific T cells met the release criteria and recognised cognate antigens in vitro. 12 patients received at least one infusion, ten received at least two, and seven received a total of three infusions. The median on-study follow-up was 109·5 days (range 23–699). All infusions were tolerated well, and no serious treatment-related adverse events were observed. Seven patients survived progressive multifocal leukoencephalopathy for longer than 1 year after the first infusion, whereas five died of progressive multifocal leukoencephalopathy within 3 months.

TABLE 2 | VSTs in clinical trials.

Target	*N*	Method of T cell selection	Antigen presentation	GVHD occurrences	CMV status	Reference/ institution
CMV	18	IFN-γ capture	Peptide mixes of pp65	3 patients with grade I aGVHD; 3 patients with grade II/III aGVHD; 3 patients with cGVHD	11 developed CMV reactivation, all responded to antivirals or repeat infusion of T cells	(46)/UCL[a]
	7	*Ex vivo* expansion	CMV lysate and peptide mixes of pp65	No GVHD	Only 1 patient had persistent CMV viremia, one reactivation after steroids; CMV-specific T cell expansion in 6 patients	(54)/MKP[b]
	14	*Ex vivo* expansion	Dendritic cells with CMV-infected fibroblasts; only CD8 clonal population infused	3 patients developed grade I/II aGVHD, all responding to steroids	No CMV disease, CMV immunity restored	(55)/FHCRC[c]
	16	*Ex vivo* expansion	Dendritic cells with CMV-infected fibroblasts	3 patients with grade I aGVHD only	8 patients also required ganciclovir but subsequently cleared viremia; 2 patients developed CMV reactivation postinfusion; CMV immunity restored	(10)/UCL
	25	*Ex vivo* expansion	CMV antigen; only CD4 clonal population infused	1 case of GVHD	7 patients with CMV reactivation; 5 patients with clinical disease; 2 patient deaths from CMV	(56)/U of Perugia[d]
	18	IFN-γ capture	pp65 protein	1 case of GVHD	4 patients died of CMV-related disease; 15 patients with *in vivo* expansion	(57)/UCH[e]
	7	*Ex vivo* expansion	Dendritic cells with peptide mixes (pp65, IE1)	No GVHD	4 patients cleared CMV; 2 with reactivation (1 associated with high dose steroids), 1 with transient increase in CMV PCR	(58)/PSHCH[f]
	9	*Ex vivo* expansion	Dendritic cells with peptide mix (pp65)	3 patients with grade III aGVHD, with one associated death; 2 patients with cGVHD	2 patients with reactivation not requiring treatment	(59)/U of Sydney[g]
	16	*Ex vivo* expansion	Dendritic cells with peptide mix (pp65)	No GVHD	14 patients cleared CMV	(60)/MSKCC[h]
	2	Streptamer-selection	PBMCs with pp65-HLA beads	No GVHD	Both cleared CMV with CMV-specific expansion	(41)/U of Ulm[i]
EBV	39	*Ex vivo* expansion	PBMCs with LCLs	No aGVHD or new cases of GVHD	EBV-specific immunity restored, clearance of viremia, no PTLD	(49)/SJCRH[j]
	10	IFN-γ capture	EBNA1 overlapping peptide mixtures	1 patient with Grade I/II aGVHD	Expansion of EBV-specific T cells in 8 patients and clinical/virologic response in 7 patients	(47)/UCH
	6	IFN-γ capture	EBV peptide mix	No GVHD	Resolution of PTLD in 3 patients; progression of PTLD in 3 patients (all late stage at time of transfer)	(63)/HZM[k]
	114	*Ex vivo* expansion	PBMCs with LCLs	No *de novo* GVHD; 8 patients with reactivation of Grade I/II GVHD; 11 patients with limited cGVHD; 2 patients with extensive cGVHD	No PTLD development; remission of preexisting PTLD in 11 of 13 patients	(48)/BCM[l]
	19	*Ex vivo* expansion	T cells with LCLs	No GVHD	Resolution of PTLD in 13 patients; 2 patients with PD received DLI and 1 achieved CR	(64)/MSKCC
	36	*Ex vivo* expansion	T cells with LCLs	No aGVHD, 4 patients with limited cGVHD	No PTLD development	(65)/SJCRH
	42	*Ex vivo* expansion	T cells with LCLs	No GVHD	No PTLD development, reconstitution of EBV-specific immunity	(66)/SJCRH
	4	*Ex vivo* expansion	PBMCs with LCLs	No GVHD	Clearance of PTLD or EBV viremia	(67)/U of Pavia[m]

(*Continued*)

TABLE 2 | Continued

Target	N	Method of T cell selection	Antigen presentation	GVHD occurrences	CMV status	Reference/ institution
Adenovirus	9	IFN-γ capture	Adenovirus antigen C	Exacerbation of preexisting skin GVHD	5 patients responded with expansion of adenovirus-specific T cells in 5 patients	(70)/UCH
	30	IFN-γ capture	Hexon protein	2 grade I GVHD; overall decrease in patients with GVHD	21 patients responded	(45)/UCH
	1	IFN-γ capture	Hexon protein	No GVHD	Complete response	(71)/BGCH[n]
BK virus	1	IFN-γ capture	Large-T, VP1	No GVHD	Complete response	(74)/HH[p]
Multivirus specific						
EBV-CMV-Adeno	10	*Ex vivo* expansion	Dendritic cells nucleofected with viral plasmids: EBV (LMP1, LMP2, bzlf), CMV (IE1, pp65), adenovirus (hexon, penton)	1 grade I/II GVHD	8 patients with CR; 1 patient with stable EBV disease without PTLD	(81)/BCM
EBV-Adeno	12	*Ex vivo* expansion	PBMCs with Ad5f35 vector and LCLs	No GVHD	Expansion of virus-specific immunity, resolution or prevention of clinical disease	(11)/BCM
EBV-CMV-Adeno	11	*Ex vivo* expansion	PBMCs with LCLs transformed with Ad5f35-CMVpp65 vector	No GVHD	Expansion of EBV- and CMV-specific immunity in all patients, adenovirus-specific immunity in patients with clinical disease; clearance of all clinical disease	(80)/BCM
EBV-CMV-Adeno-VZV	10	*Ex vivo* expansion	PBMCs with Ad5F35-pp65, Ad5F35-EBNA1/LMP, VZV vaccine	1 grade II GVHD, 1 grade III GVHD	6 patients with CMV reactivation, only one receiving antiviral therapy; no EBV, adenovirus, or VZV reactivation	(76)/U of Sydney
EBV-CMV-Adeno-BKV-HHV6	11	*Ex vivo* expansion	PBMCs with pepmixes (LMP2, BZLF, EBNA1, penton, hexon, pp65, IE-1, VP1, large T, U11, U14, U90)	1 grade II aGVHD	No viral reactivation in 3 patients infused prophylactically; EBV—5 patients with CR, including PTLD; CMV—2 patients with CR, 1 PR; adenovirus—1CR; BKV—5 patients with CR, 1 PR, 1 NR; HHV6—2 patients with CR	(75)/BCM
Third party						
EBV	8	*Ex vivo* expansion	PBMCs with LCLs	No GVHD	3 patients with CR; 1 patient with PR, subsequently refused treatment; 2 patients with no response; 2 patients passed away before evaluation (unrelated to VSTs)	(85)/U of Edinburgh[r]
EBV	33	*Ex vivo* expansion	PBMCs with LCLs	No GVHD	21 patients with CR or PR; 6 month OS 79%	(86)/U of Edinburgh
EBV-CMV-Adeno	50	*Ex vivo* expansion	PBMCs with LCLs transformed with Ad5f35-CMVpp65 vector	6 with grade I GVHD; 1 with grade II GVHD, 1 with grade III GVHD	17 of 23 with PR/CR for CMV; 14 of 18 PR/CR for adenovirus; 6 of 9 PR/CR for EBV	(22)/BCM
EBV	2	*Ex vivo* expansion	PBMCs with LCLs	No GVHD	Both with CR	(87)/MSKCC

N = number of patients in study.

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[d]*University of Perugia, Perugia, Italy.*

[e]*University Children's Hospital, Tübingen, Germany.*

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[g]*University of Sydney, Sydney, NSW, Australia.*

[h]*Memorial Sloan-Kettering Cancer Center, New York, NY, USA.*

Third-Party VSTs

- The relatively low incidence of refractory infectious complications in the post-transplantation period makes it impractical to generate viral-specific populations for all HSCT recipients at risk.

- At the same time, the aggressive nature of these infections requires rapid treatment of patients who do not respond to first line antiviral therapy. Thus, 2 week wait is too long once a patient has been identified as needing treatment. Therefore, the use of longer manufacturing approaches means that T cells need to be generated before the patient develops an infection.

- Some of the limitations in the generation and application of donor-derived viral-specific adoptive cell therapy can be overcome by using banked, off-the shelf, or so-called third party T cells.

REGULAR ARTICLE

blood advances

Virus-specific T-cell therapy to treat BK polyomavirus infection in bone marrow and solid organ transplant recipients

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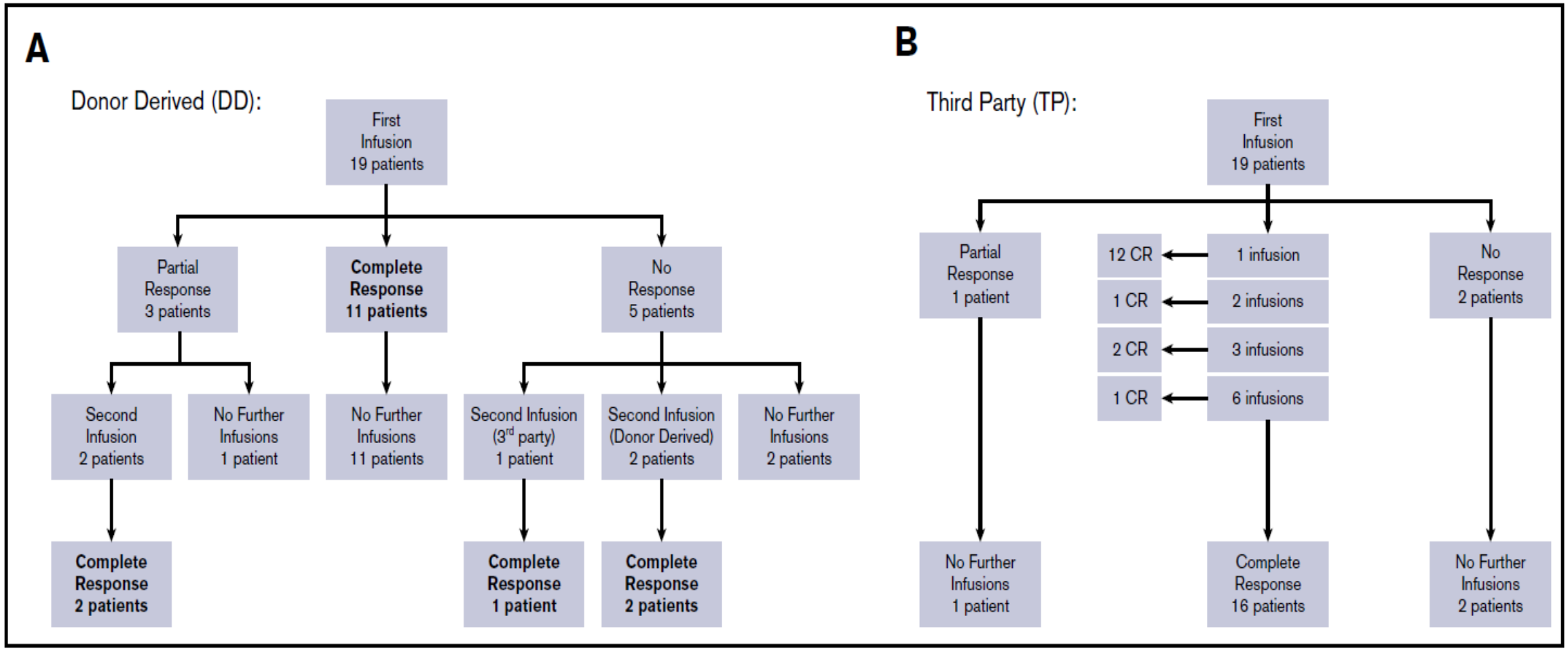

Figure 1. Response to VSTs. (A) Response to donor-derived BKPyV-VST flowchart. (B) Response to third-party BK-VST flowchart.

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ORIGINAL REPORT

Off-the-Shelf Virus-Specific T Cells to Treat BK Virus, Human Herpesvirus 6, Cytomegalovirus, Epstein-Barr Virus, and Adenovirus Infections After Allogeneic Hematopoietic Stem-Cell Transplantation

Ifigeneia Tzannou, Anastasia Papadopoulou, Swati Naik, Kathryn Leung, Caridad A. Martinez, Carlos A. Ramos, George Carrum, Ghadir Sasa, Premal Lulla, Ayumi Watanabe, Manik Kuvalekar, Adrian P. Gee, Meng-Fen Wu, Hao Liu, Bambi J. Grilley, Robert A. Krance, Stephen Gottschalk, Malcolm K. Brenner, Cliona M. Rooney, Helen E. Heslop, Ann M. Leen, and Bilal Omer

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0732-183X/17/3531w-3547w/$20.00

ABSTRACT

Purpose

Improvement of cure rates for patients treated with allogeneic hematopoietic stem-cell transplantation (HSCT) will require efforts to decrease treatment-related mortality from severe viral infections. Adoptively transferred virus-specific T cells (VSTs) generated from eligible, third-party donors could provide broad antiviral protection to recipients of HSCT as an immediately available off-the-shelf product.

Patient and Methods

We generated a bank of VSTs that recognized five common viral pathogens: Epstein-Barr virus (EBV), adenovirus (AdV), cytomegalovirus (CMV), BK virus (BKV), and human herpesvirus 6 (HHV-6). The VSTs were administered to 38 patients with 45 infections in a phase II clinical trial.

We found no correlation between viral load reduction and HLA matching in patients who received low (one to three alleles matched) versus high (four to eight matching alleles) HLA matched VST lines

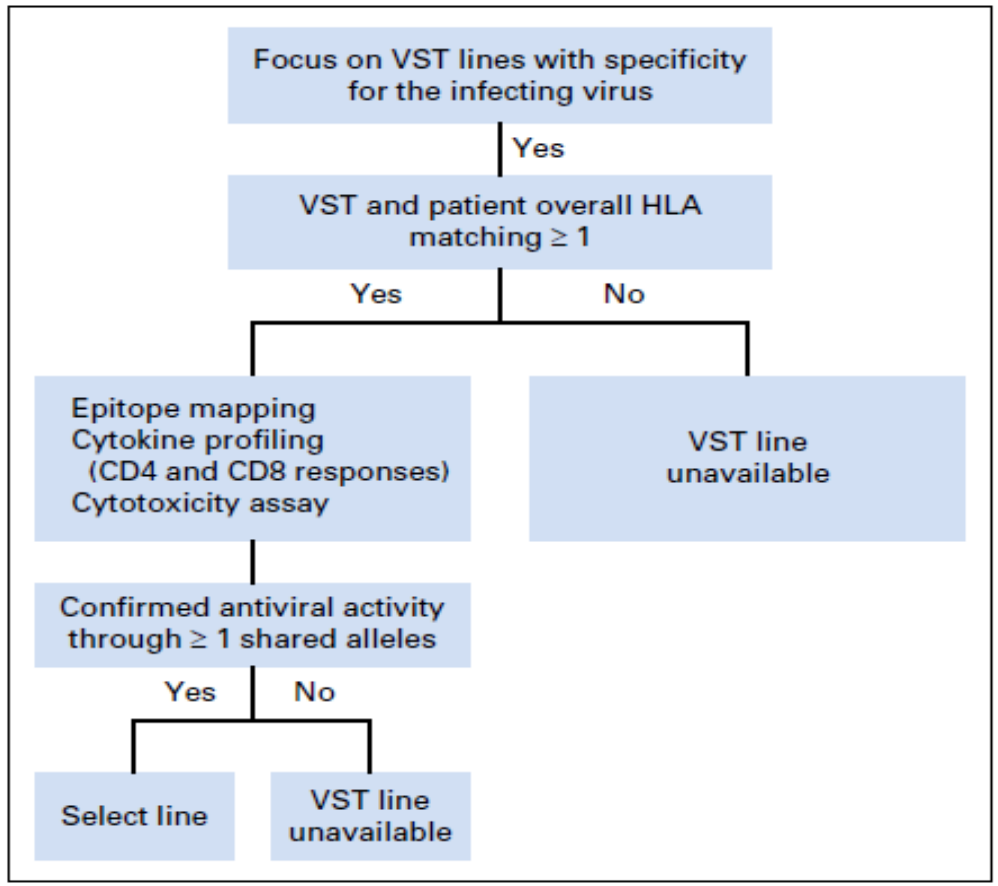

Fig A1. Decision algorithm for virus-specific T-cell (VST) selection.

Release criteria for mVSTs included

- viability >70%, negative culture for bacteria and fungi after 7 days, endotoxin testing <5 EU/ml, negative result for mycoplasma, **<10%** killing of haploidentical PHA (Sigma-Aldrich)-activated lymphoblasts at a 20:1 ratio.

Biology of Blood and Marrow Transplantation

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ASBMT American Society for Blood and Marrow Transplantation

Cellular Therapy

Establishment and Operation of a Third-Party Virus-Specific T Cell Bank within an Allogeneic Stem Cell Transplant Program

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A B S T R A C T

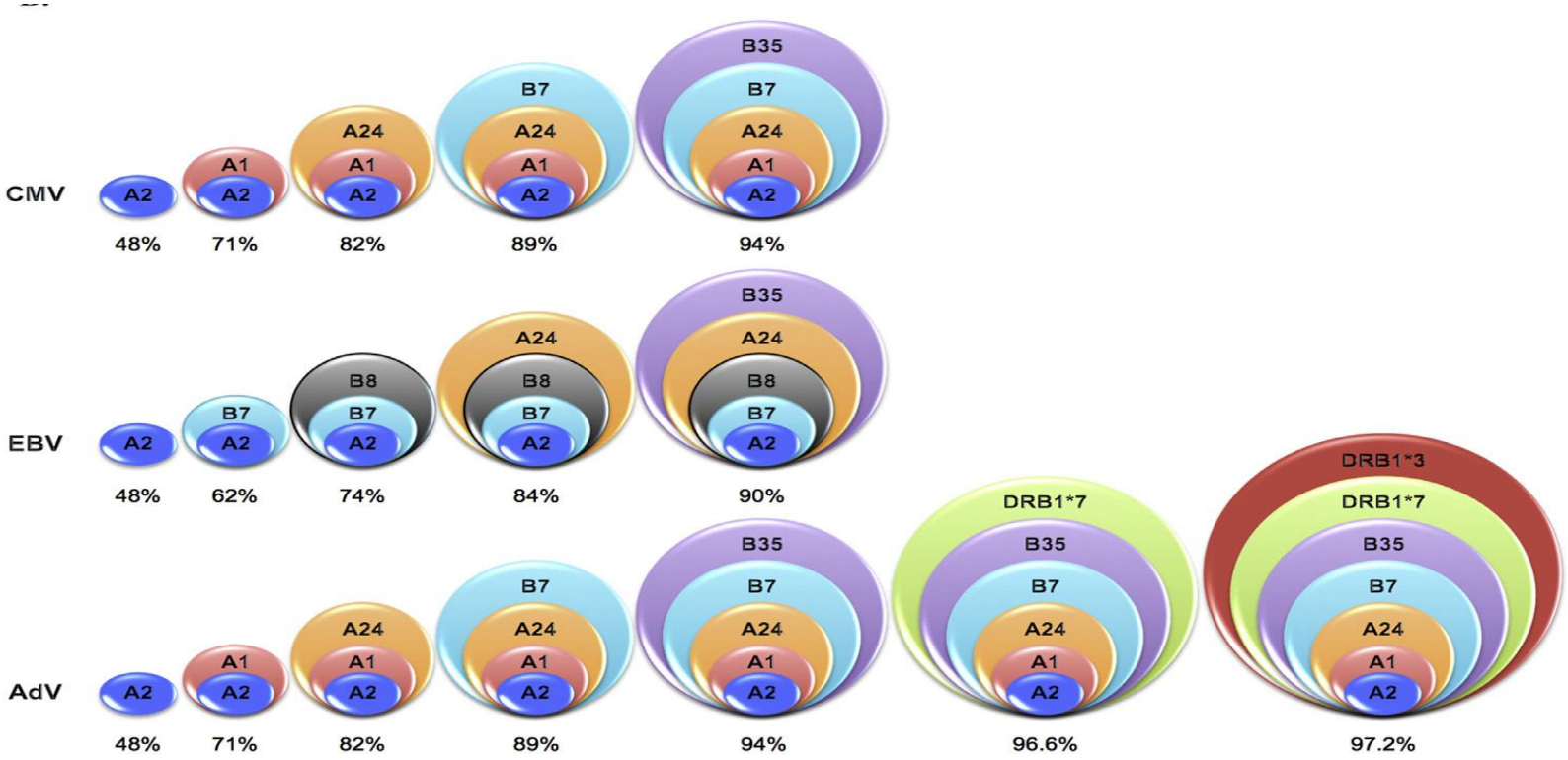
Hematopoietic stem cell transplantation (HSCT) donor–generated virus-specific T cells (VSTs) can provide effective treatment for viral infection post-HSCT but are not readily accessible to all patients. Off-the-shelf cryopreserved VSTs suitable for treatment of multiple patients are an attractive alternative. We generated a bank of 17 cytomegalovirus (CMV)–, 14 Epstein-Barr virus (EBV)–, and 15 adenovirus (AdV)–specific T cell products from 30 third-party donors. Donors were selected for expression of 6 core HLA antigens expressed at high frequency in the local transplant population. T cells were generated by co-culturing venous blood or mobilized hematopoietic stem cell (HSC)–derived mononuclear cells with monocyte-derived dendritic cells pulsed with overlapping pepti-

- A particularly desirable attribute of therapy using third-party VST banks is the reduced requirement for HLA matching between product and recipient.

- In contradistinction to banks of hematopoietic progenitor cells that must contain large numbers of products to provide a reasonable chance of HLA matching, data from a number of studies confirm the efficacy of partially HLA-matched third-party VSTs.

- Only a small number of carefully selected third party donors are required to generate a VST bank of broad coverage, indicating the feasibility of local banking integrated into existing allogeneic HSCT programs.

- We utilized the frequency of HLA types in our HSCT population to direct the recruitment of donors for our bank



Third-party donor selection targeting specific HLA antigens.

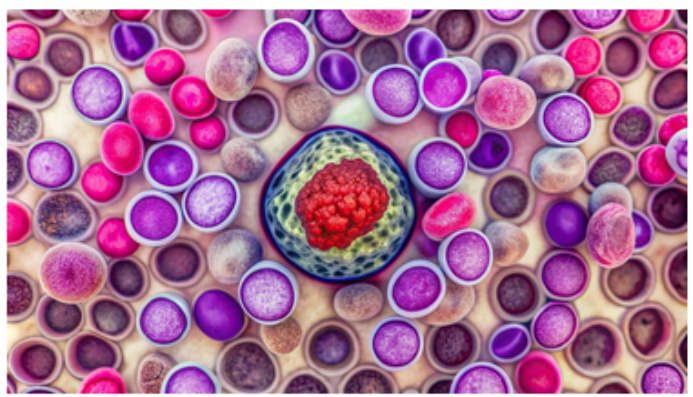
FDA Accepts Application of Tab-Cel, First-in-Class Therapy for EBV+ PTLD

July 17, 2024

The FDA has accepted and granted priority review to tab-cel, a treatment for Epstein Barr virus-positive posttransplant lymphoproliferative disease.

- **The FDA has accepted and granted priority review to the biologics license application (BLA) of tabelecleucel (tab-cel; Ebvallo) for the treatment of Epstein-Barr virus-positive (EBV+) posttransplant lymphoproliferative disease (PTLD).**
- **A Prescription Drug User Fee Act (PDUFA) target action date of January 15, 2025, has been set.**
- **If approved, tab-cel would become the first FDA-approved therapy in the US for EBV+ PTLD.**

$143,900 to $273,700 per treatment cycle



Close-up of hematopoietic niche in bone marrow: ©artsakon - stock.adobe.com


THANK YOU!

- The phase 3 ALLELE trial showed a 50.7% overall response rate and a 28.0% complete response rate in EBV-positive PTLD patients.

BK virus-specific T cells for immunotherapy of progressive multifocal leukoencephalopathy: an open-label, single-cohort pilot study

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Summary

Background Progressive multifocal leukoencephalopathy, a rare disease of the CNS caused by JC virus and occurring in immunosuppressed people, is typically fatal unless adaptive immunity is restored. JC virus is a member of the human polyomavirus family and is closely related to the BK virus. We hypothesised that use of partly HLA-matched donor-derived BK virus-specific T cells for immunotherapy in progressive multifocal leukoencephalopathy would be feasible and safe.

Methods We did an open-label, single-cohort pilot study in patients (aged 18 years or older) with clinically definite progressive multifocal leukoencephalopathy and disease progression in the previous month at the National Institutes of Health (NIH) Clinical Center (Bethesda, MD, USA). Overlapping peptide libraries derived from large T antigen and major capsid protein VP1 of BK virus with high sequence homology to JC virus counterparts were used to generate polyomavirus-specific T cells cross-recognising JC virus antigens. Polyomavirus-specific T cells were manufactured from peripheral blood mononuclear cells of first-degree relative donors aged 18 years or older. These cells were administered to patients by intravenous infusion at 1×10^6 polyomavirus-specific T cells per kg, followed by up to two additional infusions at 2×10^6 polyomavirus-specific T cells per kg. The primary endpoints were feasibility (no manufacturing failure based on meeting release criteria, achieving adequate numbers of cell product for clinical use, and showing measurable antiviral activity) and safety in all patients. The safety monitoring period was 28 days after each infusion. Patients were followed up with serial MRI for up to 12 months after the final infusion. This trial is registered at ClinicalTrials.gov, NCT02694783.

Findings Between April 7, 2016, and Oct 19, 2018, 26 patients were screened, of whom 12 were confirmed eligible and received treatment derived from 14 matched donors. All administered polyomavirus-specific T cells met the release criteria and recognised cognate antigens in vitro. 12 patients received at least one infusion, ten received at least two, and seven received a total of three infusions. The median on-study follow-up was 109·5 days (range 23–699). All infusions were tolerated well, and no serious treatment-related adverse events were observed. Seven patients survived progressive multifocal leukoencephalopathy for longer than 1 year after the first infusion, whereas five died of progressive multifocal leukoencephalopathy within 3 months.

Interpretation We showed that generation of polyomavirus-specific T cells from healthy related donors is feasible, and these cells can be safely used as an infusion for adoptive immunotherapy of progressive multifocal leukoencephalopathy. Although not powered to assess efficacy, our data provide additional support for this strategy as a potential life-saving therapy for some patients.

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See Comment page 589

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