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ARTICLE

Cytotect®CP as salvage therapy in patients with CMV infection following allogeneic hematopoietic cell transplantation: a multicenter retrospective study

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Abstract

Cytomegalovirus is one of the main contributing factors to high mortality rates in patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT). The main factors of treatment failure are both drug resistance and intolerance. In some cases, Cytotect®CP CMV-hyperimmune globulin is used as salvage therapy. This study aims to investigate the safety and efficacy of Cytotect®CP as a salvage therapy in patients with CMV infection after allo-HCT. Twenty-three consecutive patients received Cytotect®CP for CMV infection after prior CMV therapy. At the time of Cytotect®CP introduction, 17 patients (74%) had developed acute GVHD and 15 patients (64%) were receiving steroid treatment; Cytotect®CP was used as monotherapy ($n = 7$) and in combination ($n = 16$). Overall, response was observed in 18 patients (78%) with a median time of 15 days (range: 3–51). Of the 18 responders, 4 experienced CMV reactivation, while 5 responders died within 100 days of beginning treatment. Of these 5 deaths, 4 were due to causes unrelated to CMV. Estimated 100-day OS from the introduction of Cytotect®CP was 69.6%. No statistically significant difference was observed in 100-day OS between responders and non-responders (73.7% vs 50.0%, $p = 0.258$). Cytotect®CP as salvage therapy is effective and well-tolerated. Given its safety profile, early treatment use should be considered.

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is still the only curative option for patients with certain hematological diseases[1–4].

Cytomegalovirus (CMV) is a common virus in human populations, and many individuals are carriers of the virus by the time of adulthood. Like all herpes viruses, CMV establishes a lifelong latency in the host, but a person with a healthy immune system will rarely experience signs or symptoms of the virus. However, in cases of

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individuals with a compromised immune system, such as patients undergoing allo-HCT, there is a serious risk of CMV infection, activation, or reactivation[5, 6]. Therefore, CMV is one of the greatest causes for concern post- transplant[6, 7].

Delayed post-transplant immune reconstitution combined with prophylactic immunosuppressive treatment for graft versus host disease (GVHD) creates conditions for CMV reactivation[8–11]. A suppressed immune system that leads to a lack of CMV-specific response from $CD8^+$ T cells predisposes a patient to CMV infection[12, 13].

CMV infection treatment is commonly based on ganciclovir and foscavir and, to a lesser extent, on other drugs including cidofovir[6]. However, these drugs cause high levels of toxicity which result in myelotoxicity, in the case of ganciclovir, or, in the case of foscavir and cidofovir, potential renal failure, incurring treatment discontinuation.

CMV treatment failure, a major issue in patients showing signs of infection, may occur in up to 55% of patients and 45% of treatment episodes. The risk of treatment failure may be higher during first-line treatment and during the use of immunosuppressive medication, as is predominantly the case for patients undergoing allo-HCT[14].

Treatment failure may be caused by drug resistance, developed through certain mutations, and by antiviral intolerance leading to treatment discontinuation[6, 15, 16]. Although drug resistance is not common after allo-HCT, it can occur with all anti-viral agents used for CMV prophylaxis and therapy and must be suspected in patients who increase their CMV load for more than 2 weeks despite a well-conducted therapy. Because ganciclovir and its prodrug, valganciclovir, are used as first-line agents in approximately 90% of patients[17], most studies on resistance have been reported on ganciclovir resistance. Many mutations have been mapped, and genotypic assays are available for diagnostic analysis in reference laboratories [18, 19].

Cellular and humoral immune mechanisms are involved in the immune response to CMV infection[20]. Cytotect®CP, also called CMV hyperimmune globulin, contains a high titer of anti-CMV polyclonal antibodies, was developed and licensed in the 1980s for CMV disease prophylaxis[21]. However, the use of Cytotect®CP is currently limited in most French transplantation centers to salvage therapy for recurrent and refractory CMV infections, and, in some cases, in combination for CMV pneumonia[22–24].

Since 2010, Cytotect®CP has been authorized in the European Union and other countries for the prophylaxis of clinical manifestations of CMV infection in patients receiving immunosuppressive treatment, particularly transplant recipients.

This study aims to investigate the safety and efficacy of Cytotect®CP as a salvage therapy in patients with CMV infection after allo-HCT.

Patients and methods

This multicenter study was conducted according to the Declaration of Helsinki. Written consent to use medically relevant data for research purposes was obtained from each patient and donor before transplant.

Between February 2015 and November 2016, 23 adult patients who had received Cytotect®CP as salvage therapy for CMV infection after allo-HSCT in eight centers across France were included.

Refractory CMV infection was defined as CMV DNAemia lasting for >2 weeks in spite of administration of a full dose of antiviral drug therapy. Very-high risk CMV patient was defined as patient who has a pre-HCT history of 2 or more CMV infection episodes (1 patient). Recurrent infection was defined as new detection of CMV infection in a patient who had previously documented infection and in whom DNAemia remained undetectable for a period of at least 4 weeks during surveillance.

No patient received specific anti-CMV prophylaxis except for valacyclovir, which has not been proven to have an effect on CMV.

GVHD prophylaxis was conducted according to the SFGM-TC guidelines[25]. Of note, 16 (70%) patients had received antithymoglobulin within the conditioning regimen. Quantitative polymerase chain reaction (PCR) was used to quantify CMV viral load (DNAemia) in blood. The SFGM-TC (Francophone Society of Bone Marrow Transplantation and Cellular Therapy) guidelines were used for the cut-off for when to begin treatment (i.e., >3–3.5 log UI/mL)[6, 26].. At least once a week, CMV viral load was monitored.

Cytotect®CP was given either at prophylaxis dose (200 U/kg/week) to prevent CMV recurrences or as preemptive therapy (400 U/kg on days 1, 4, 8 then 200 U/kg on days 12 and 16).

Statistical analysis

Given that many factors can affect survival of allo-HCT, we restricted our analyses to 100-day overall survival (OS) to better identify the impact of CMV infection on survival. The definition of 100-day OS was determined to be the interval from the beginning of Cytotect®CP therapy to death within 100 days, regardless of the cause of death. Survival curves and rates were generated and estimated using the Kaplan–Meier method. All statistical analyses were performed using SPSS® (SPSS Inc., Chicago, IL, USA).

Table 1 patients and donors' characteristics at transplant and transplantation modalities

Total number of observations, No (%)	23 (100)
Recipient age, median years (range)	53.1 (19,7-69.9)
Recipient gender	
Male	11 (48)
Female	12 (52)
Donor gender	
Male	14 (61)
Female	9 (39)
Sex mismatch[a], No (%)	5 (22)
CMV serology	
Recipient positive and donor positive	5 (22)
Recipient positive and donor negative	16 (70)
Recipient negative and donor positive	2 (9)
Recipient negative and donor negative	0
Underlying disease status at transplant, No (%)	
Complete remission (CR)	13 (57)
Improvement/partial remission (PR)	4 (17)
Stable disease or untreated (SD)	1 (4)
Relapse/progression (RR)	5 (22)
Donor type, No (%)	
Identical sibling	4 (17)
Haploidentical	5 (22)
Matched unrelated	12 (52)
Mismatched unrelated	2 (9)
Source of stem cells, No (%)	
Bone marrow (BM)	4 (17)
Peripheral blood (PB)	19 (83)
Conditioning regimen, No (%)	
Myeloablative (MA)	8 (35)
Reduced intensity (RIC)	15 (65)
Anti-thymoglobulin within conditioning, No (%)	
No	7 (30)
Yes	16 (70)
Total body irradiation, No (%)	
No	18 (78)
Yes	5 (22)
GVHD prophylaxis, No (%)	
Ciclosporine-A (CS-A)	2 (9)
CS-A - Mycophenolate Mofetil (MMF)	9 (39)
CS-A - Methotrexate (MTX)	7 (30)
Post_Cy – CS-A and MMF[b]	5 (22)
Anti-viral prophylaxis, No (%)	
Valacyclovir	23 (100)

[a] Female donor and male recipient

[b] post-transplant cyclophosphamide

Table 2 patients' condition at the introduction of CytotectCP®

Total number of observations, No (%)	23 (100)
History of acute GVHD, No (%)	
Grade 0	6 (18)
Grade I	0
Grade II	6 (18)
Grade III-IV	11 (64)
History of chronic GVHD, No (%)	
Grade 0	16 (70)
Limited	3 (13)
Extensive	4 (17)
Active GVHD at the time of Cytotect®, No (%)	11 (49)
Steroids at the time of Cytotect®, No (%)	15 (65)

Results

Median age of patients at transplant was 53.1 years (range 19.7-69.9). Patient, donor and disease characteristics as well as transplantation modalities are shown in Table 1.

As shown in Table 2, 17 patients (74%) had developed acute grade II GVHD ($n = 6$), acute grade III-IV ($n = 11$), limited chronic GVHD ($n = 3$) and extensive chronic GVHD ($n = 4$) before the introduction of Cytotect®CP. While 11 (49%) had an active GVHD when beginning Cytotect®CP therapy, 15 (64%) patients were still receiving steroids.

Median time of CMV first reactivation was 35 days (range, 17–188) after allo-HCT and median peak of CMV load was 4 $\log_{10}$ at the first episode in patients who received Cytotect®CP as a salvage therapy. The median time from transplant to initial Cytotect®CP administration was 151 days (range: −30 to +587).

One patient with a long history of pre-transplant refractory CMV infection received Cytotect®CP as prophylaxis (from day −30 before transplant). Two other patients received Cytotect®CP as preemptive treatment, but following a post-transplant prophylaxis scheme along with other anti-CMV therapies for a history of recurrent CMV infection. All other patients received Cytotect®CP as preemptive therapy after transplantation and according to the aforementioned preemptive scheme.

As shown in Table 3, Cytotect®CP was given during the first CMV episode ($n = 5$), second episode ($n = 5$), and successive episodes ($n = 12$).

Cytotect®CP was used as an intravenous monotherapy in 7 patients: 6 patients whose CMV infection was refractory to 2 adequate lines of treatment or more, and the aforementioned prophylaxis patients, while it was added to: ganciclovir ($n = 5$), foscavir ($n = 5$), both ganciclovir and foscavir ($n = 2$), and other combinations ($n = 4$) when response to the aforementioned treatments alone was not satisfactory.

Table 3 CytotectCP® use and patients outcomes

Total number of observations, No (%)	23 (100)
Use of Cytotect®, No (%)	
Primary Prophylaxis	1 (4)
First episode	5 (22)
Second episode	5 (22)
Third episode	7 (30)
≥Four episodes	5 (22)
Use of Cytotect®, No (%)	
Monotherapy	7 (30)
Combination with Gancyclovir	5 (22)
Combination with Foscavir	5 (22)
Combination with Gancyclovir and Foscavir	2 (9)
Other combination	4 (17)
Time to first CMV reactivation, median (range)	35 days (17–188)
Peak viral load at first episode, log (range)	4 (0–6,6)
Time from transplant to Cytotect® onset, median (range)	151 days (−30–587)
Cytotect® scheme	
Prophylactic (200 U/kg/3Weeks)	3 (13)
Preemptive (400 U/kg on days 1, 4, 8 then 200 U/ kg on days 12 and 16)	20 (87)
Response to Cytotect® #1, No (%)	
Negative CMV PCR	16 (70)
VGPR[a]	1 (4)
Persistent negative CMV PCR	1 (4)
Failure	4(18)
Not evaluable for early death	1 (4)
Time to response in responders, median (range)	17 days (3-69)
CMV relapse after Cytotect®, days	3/17 (18)
Time to relapse, days	17, 23, 66
Death within 100 days after Cytotect®	8 (35%)
Causes of death, total	8 (100)
Related to CMV	1 (13)
GVHD	3 (37)
Other infections	3 (37)
Relapse of the underlying disease	1 (13)

[a] VGPR: very good partial response (one patient decreased CMV from 4.8 $\log_{10}$–3.6 $\log_{10}$)

Overall response to Cytotect®CP was observed in 18 (78%) patients of whom 16 experienced conversion to negative CMV-PCR, one demonstrated a decrease in viral load from 4.8 log to 3.6 log IU/ml, and one persisted in showing negative CMV-PCR after having received the drug as prophylactic treatment. For this patient, the absence of CMV reactivation, despite a long pre-transplant history of CMV infection, has been considered a success. The median time to achieve a CMV-PCR response was 15 days (range, 3-51). Treatment has been recorded as failure in 4 patients.

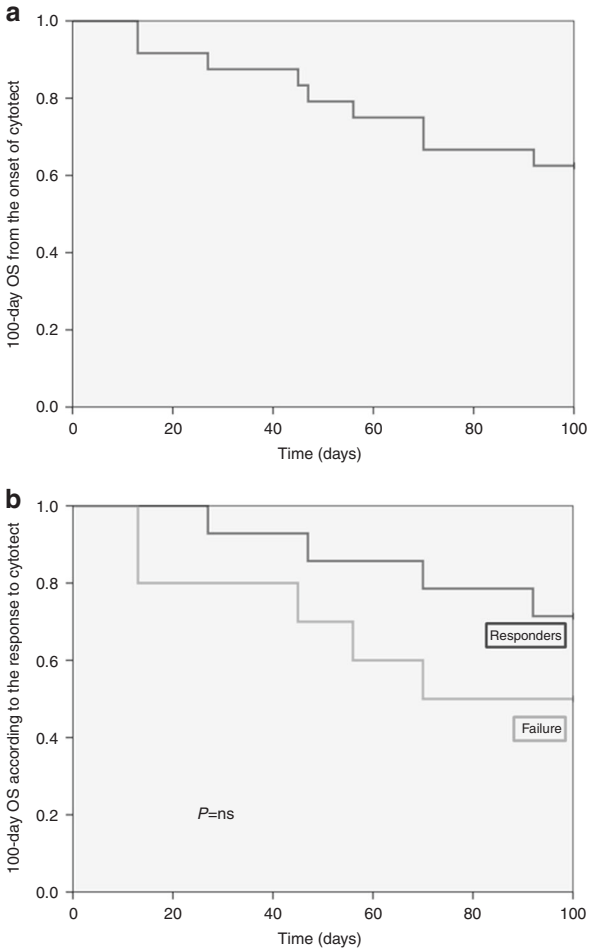

Fig. 1 Overall survival in 23 patients 100 days after outset of Cytotect®CP (2 deaths were related to CMV while 6 others were unrelated to CMV). **a** 100-day from the onset of CytotectCP® overall survival in the 23 patients. (2 deaths were related to CMV while 6 others were unrelated to CMV). **b** 100-day overall survival according to the response to CytotectCP®

The response was non-evaluable in one patient who died 13 days after the introduction of Cytotect®CP (Table 3).

The treatment was well-tolerated with no clinically significant adverse events.

Four out of the 18 responders experienced CMV relapse 9–49 days after the date of best response. Five patients who responded to the drug died within 100 days after the introduction of Cytotect®CP due to the following causes: GVHD ($n = 2$), other infection ($n = 1$), underlying disease ($n = 1$), and CMV-related causes ($n = 1$). Two out of the 4 non-responders died of other infection ($n = 1$) and GVHD ($n = 1$). One patient died of another infection 13 days after starting Cytotect®CP therapy.

Estimated 100-day OS from the introduction of Cytotect®CP was 69.6 % (Fig. 1a). There was no statistical difference in 100-day OS between patients who responded to Cytotect®CP and those who did not (73.7% versus 50.0%, $p = 0.258$) (Fig. 1b).

Table 4 Individual characteristics of patients and outcome

Patient#	Sex/ age (years)	CMV serostatus	ATG	aGVHD/ cGVHD	Steroids > 0.5 mg/kg[a]	Episode of CMV infection[a]/CMV load[a]	Days transplant to Cytotect®	Use of Cytotect®	Response	time to response	CMV relapse/ days[b]	Status/ causes of death at day 100
#1	F/51	R+/D−	yes	3/ext	yes	3/4.2	506	mono	negative PCR	3	yes/14	died/GVHD
#2	F/61	R+/D−	yes	3/ext	yes	>3/5.7	465	com/fos	VGPR[c]		no	alive
#3	M/20	R+/D+	yes	2/ext	yes	>3/3.4	587	other	negative PCR	4	no	alive
#4	M/31	R+/D−	yes	0/0	no	2/4.9	59	com/gan	negative PCR	27	no	alive
#5	M/65	R+/D+	no	3/ext	yes	3/4.1	164	com/gan	negative PCR	14	no	alive
#6	M/31	R+/D-	no	3/0	yes	>3/3.8	542	mono	negative PCR	3	no	died/other inf
#7	M/61	R−/D+	yes	0/0	no	3/3.3	230	mono	negative PCR	14	no	alive
#8	F/62	R+/D+	yes	2/0	yes	3/4.2	245	com/gan	NE		–	died/other inf
#9	F/68	R+/D+	no	2/0	yes	3/4.2	176	com/fos	negative PCR	4	no	alive
#10	M/57	R+/D−	no	2/lim	yes	3/3.4	280	mono	negative PCR	69	–	alive
#11	F/47	R+/D−	no	4/0	no	1/5.6	58	com/fos	negative PCR	19	yes/11	died/UD relapse
#12	F/45	R+/D−	no	3/0	yes	1/4.2	99	com/gan	negative PCR	15	no	alive
#13	M/64	R+/D−	yes	0/0	no	1/4.2	81	com/Fos+cid	Fail		–	alive
#14	M/53	R+/D−	yes	4/0	yes	2/3.6	151	com/fos	negative PCR	22	no	alive
#15	F/70	R+/D−	yes	2/0	no	3/5.9	196	com/Fos +gan	Fail		–	alive
#16	F/44	R+/D−	yes	0/0	no	2/5.5	123	mono	negative PCR	51	no	alive
#17	F/63	R−/D+	yes	4/0	yes	2/4.1	119	com/gan	Fail		–	died/other inf
#18	F/42	R+/D−	yes	0/0	yes	2/3.5	171	mono	negative PCR	17	yes/49	alive
#19	F/44	R+/D−	yes	3/0	yes	1/4	111	other	Fail		–	died/GVHD
#20	M/63	R+/D+	no	2/0	yes	1/4.4	71	com/fos	negative PCR	18	yes/9	Died/CMV
#21	M/48	R+/D−	yes	3/lim	yes	>3/3.8	47	com/Fos +gan	negative PCR	21	no	died/GVHD
#22	F/58	R+/D−	yes	0/0	no	>3[d]/NA	-30	mono	Sustained neg	27	no	alive
#23	M/37	R+/D−	yes	4/lim	no	>3/3.1	35	other	negative PCR	6	no	alive

CMV-R recipient positive CMV serology at transplant, *CMV-D* donor positive CMV serology at transplant, *ATG* antithymoglobulin, *aGVHD/cGVHD* history of acute/chronic graft-versus-host disease before the onset of Cytotect®CP, *F* female, *M* male, *ext* extensive, *lim* limited, *mono* monotherapy, *com* combination, *fos* foscavir, *gan* ganciclovir, *cid* cidofovir, *inf* infection, *UD* underlying disease, *NA* not applicable

[a] at the onset of Cytotect®CP

[b] from the time of best response

[c] this patient experienced a CMV load reduction from 4.8 $\log_{10}$ to 3.6 $\log_{10}$ and considered as having a very good partial response

[d] this patient had a long pre-transplant history of CMV and received Cytotect®CP as a prophylactic treatment during the transplant.

Table 4 summarizes individual patient characteristics and outcome.

Discussion

To the best of our knowledge, this is the first study that investigated the safety and efficacy of Cytotect® CP, CMV hyperimmune globulin, as salvage treatment in patients with CMV infection post allo-HCT.

Our major finding is that Cytotect®CP seems to be effective with 78% of overall response rate (ORR) and 69.6% of estimated 100-day OS. In addition, it was well-tolerated in all patients without any serious adverse event.

Antiviral agents used to treat CMV infections are generally reputed to cause significant side-effects. These agents can prevent full immunological post-transplant reconstitution and cause profound cytopenias. Some agents can be responsible for renal impairment which prevents immunosuppressive treatment continuation; this is especially the case with calcineurin inhibitors in allo-HCT patients. As a matter of fact, compared with a placebo, intravenous ganciclovir has been demonstrated to reduce the risk of CMV infection and disease, but did not seem to improve overall survival[13, 17, 27–29]. However, it is responsible for 30% of severe neutropenia in allo-HCT patients, increasing the risk of bacterial and fungal coinfections[13, 17, 27–30].

In case of documented or suspected resistance or intolerance to ganciclovir, foscarnet, another anti-CMV agent, is generally used as second-line agent. This drug is known also to cause many side effects, such as impaired renal function and neutropenia, especially in allo-HCT patients [18, 19, 31, 32].

Cidofovir has an anti-CMV activity against some ganciclovir-resistant isolates. Therefore, it is usually used as a third-line therapy in patients with refractory CMV infection. Like foscavir, cidofovir is responsible for renal failure and, to a lesser extent, cytopenias[33, 34].

With its safety profile, Cytotect®CP offers an alternative option for CMV infection treatment which avoids renal and bone marrow impairment. Although, the use of IVIg has not been recommended in the European Conference on Infections in Leukemia 7 based on two major studies[24, 35], those publications were objected by others[36]. Indeed, according to the SFGM-TC guidelines, CMV-specific immunoglobulins are recommended as an alternative in second line treatment, and listed also as a therapeutic option in third line treatment[26].

Though drug resistance caused by mutations in the target genes for the antiviral agent used is not the only reason of treatment failure, drug resistance should be suspected if the viral load increases in patients who have received previous antiviral therapy, and thus treatment must be adapted[13, 37].

Our study aimed to evaluate the efficacy and safety of Cytotect®CP in patients with CMV infection after allo-HCT. In fact, hyperimmune anti-CMV polyclonal antibodies activity has been explained in other clinical settings by its ability to counteract the virus with high avidity antibodies and possibly through cellular immunological reaction modulation mediated by cytokines, Fab-mediated actions, targeting Fc receptors, interactions with dendritic cells, B and T cell implication, and intracellular signal transduction blockade[22, 38, 39]. Interestingly, other studies concluded that this treatment, applied after allo-HCT, reduced the risk of CMV infection from 62 to 36% and may be effective in such patients[23, 40, 41].

Despite its retrospective nature and the small number of patients, our study demonstrates the efficacy of Cytotect®CP with 78% of ORR in patients at high risk of developing recurrent/refractory CMV infection after allo-HCT. Indeed, all patients were CMV serostatus positive at transplant and 70% of them received transplant from a CMV serostatus negative donor. The combination (recipient positivity / donor negativity) has been reported to be a risk factor of developing recurrent CMV infection after allo-HCT[42, 43]. In addition, 22% ($n = 5$) and 61% ($n = 14$) of patients received allo-HCT from a haploidentical or unrelated donor, which is another known factor for developing recurrent CMV infection[44]. Furthermore, 70% ($n = 16$) of our patients received ATG within the conditioning which can be another risk factor for CMV[45]. Seventeen patients (74%) in our study had a history of acute and/or chronic GVHD. In keeping with the findings of other publications, this fact may highlight the role of immunosuppressive treatment in CMV reactivation and the development of drug resistance and drug intolerance[46, 47].

Conclusion

In conclusion, Cytotect®CP as salvage therapy seemed to be effective in patients with CMV infection after allo-HCT. Given its safety profile and that it is less toxic to the patient than the more commonly used treatments Cytotect®CP should be considered as prophylaxis in select patients whose profiles reveal a known predisposition to CMV infection. A large prospective study is needed to confirm safety and efficacy results.

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Compliance with ethical standards

Conflict of interest IYA received honorarium from Biotest, the company that commercialize Cytotect®CP. Biotest has also provided grant for this study. The remaining authors declare that they have no conflict of interest.

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