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Short Communication

Success and failure of artesunate treatment in five transplant recipients with disease caused by drug-resistant cytomegalovirus

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ABSTRACT

Cytomegalovirus (CMV) strains resistant to ganciclovir, cidofovir and/or foscarnet were genotypically and phenotypically characterised in two haematopoietic stem cell transplant recipients and three solid-organ transplant recipients with CMV disease. The anti-malaria drug artesunate led to a favourable virological and clinical response in three cases with mild CMV diseases (fever and neutropaenia) but was ineffective in two fatal CMV diseases with lung involvement in spite of a decrease in the CMV DNA load in blood and bronchoalveolar fluid.

Multidrug resistance of cytomegalovirus (CMV) against the commercially available antiviral drugs (i.e. valaciclovir (VACV), ganciclovir (GCV)/valganciclovir (VGCV), cidofovir (CDV) and foscarnet (FOS)) characterised by amino-acid substitutions within the viral phosphotransferase (UL97) and/or the viral DNA polymerase (UL54) is a difficult challenge in haematopoietic stem cell or solid-organ transplantations (HSCT, SOT) (Boeckh and Ljungman, 2009; Kotton et al., 2010; Chou, 2008; Scott et al., 2007). The anti-malarial drug artesunate has demonstrated *in vitro* antiviral activity against multidrug-resistant CMV (Chou et al., 2011; Härter and Michel, 2012; He et al., 2012). Currently, clinical reports of treating drug-resistant CMV infections with artesunate are rare and controversial (Shapira et al., 2008; Lau et al., 2011; Wolf et al., 2011). Here we report five cases of virologically-confirmed drug-resistant CMV diseases in HSCT and SOT treated with artesunate with either favourable (three cases) or unfavourable (two cases) outcomes.

1. Reports of three cases with favourable outcomes

A 47-year-old female patient received a phenoidentical HSCT in 2007 for acute myeloid leukaemia (Table 1, patient 1). She was CMV-seropositive and the donor was CMV-seronegative (R+/D−). Valaciclovir (500 mg bid) was given from day 1 (D1) for herpes simplex prophylaxis. CMV DNA in whole blood (WB) was detected without symptoms of CMV disease on D27 by qPCR performed as described elsewhere (Gault et al., 2001). A preemptive treatment with VGCV (450 mg bid, 21 days) resulted in undetectable CMV DNA load (CMV DL) and two further episodes of asymptomatic CMV reactivation on D93 and D336 were successfully treated with VGCV (450 mg bid) (Fig. 1). On D420, within the treatment of chronic graft-versus-host disease, fever, myelosuppression and a significant increase of CMV DL were unsuccessfully treated with different anti-CMV regimens over the following 6 months (FOS 100 mg/kg/day, CDV 5 mg/kg/week, intravenous (IV) GCV 5 mg/kg bid). On D576, the direct PCR sequencing of the *UL97* and *UL54* genes performed by the French national reference center for CMV revealed drug-resistant CMV in blood with a C592G substitution in *UL97* responsible for low-level GCV resistance, associated with two substitutions in *UL54*: L545S conferring GCV and CDV cross-resistance and D588N known to confer resistance to

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Table 1
Patient characteristics.

	TX[a]	CMV[c] antibody status (D/R[d])	Onset of CMV infection from TX[a] (days)	Anti-viral treatment received	Peak VL[f] in whole blood (log copies/mL)	Symptoms	Time to characterisation of virological resistance (days from TX[a])	Resistance mutation to GCV: *UL97*	Resistance mutation to anti-virals: *UL97*	Phenotypic resistance (SI_{50})[h]	Clincal and virological outcome	Time to undetectable VL[f] under artesunate treatment
Patient 1	HSCT[b]	D−/R+	27	VACV, VGCV, GCV, CDV, FOS[e]	>4	Fever, neutropaenia	576	C592G	L545S, D588N	GCV (3.7), CDV (3.1), FOS (3.4)	CMV viraemia neg[i], favourable[j]	1 month
Patient 2	Lung	D+/R−	472	VGCV, GCV[e]	>4	Fever, neutropaenia	543	None	L545S	GCV (3.4), CDV (8.4)	CMV viraemia neg[i], favourable[j]	3 months
Patient 3	Lung	D+/R−	347	VGCV, GCV[e]	>4	Fever, neutropaenia	536	A594V	None	GCV (3.7)	CMV viraemia neg[i], favourable[j]	1 month
Patient 4	Kidney	D+/R−	55	VGCV, GCV, FOS[e]	>5 (BAL[g]>4)	Pneumonia	113	C592G	A987G, N408K, G841A	GCV (7.7), CDV (5.7), FOS (3.9)	Unfavourable, death	
Patient 5	HSCT[b]	D+/R+	124	VGCV, GCV, FOS[e]	>7 (BAL[g]>7)	Pneumonia	261	L595S, M460I, 601–603 deletion	None		Unfavourable, death	

[a] Tx, transplant.
[b] HSCT, haematopoietic stem cell transplant.
[c] CMV, cytomegalovirus.
[d] D/R, donor/recipient.
[e] VACV, valaciclovir; GCV, ganciclovir; VGCV, valganciclovir; CDV, cidofovir; FOS, foscarnet.
[f] VL, viral load.
[g] BAL, broncho-alveolar fluid.
[h] SI_{50} = sensitivity index = IC_{50} of the isolate/IC_{50} of AD169 reference strain.
[i] CMV viraemia neg, means that DNAemia became negative after artesunate treatment (alone or in association).
[j] Favourable clinical outcome, means no further clinical events attributable to CMV infection.