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Study of cytomegalovirus resistance in allogeneic stem cell transplant patients (Hospital de la Princesa, Madrid, Spain)

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OBJETIVES: Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality in inmunocompromised patients, especially in allogeneic stem cell transplanted (allo-SCT). Antiviral resistance is emerging and is related to mutations in different CMV genes (polymerase or protein kinase). We analyze the CMV infection, treatment and resistance in five allo-SCT patients with virus reactivation in the context of severity of the disease with a lethal progression in all cases.

PATIENTS/METHODS: All patients, after CMV reactivation, had an early treatment for long periods with Ganciclovir (patients 1 and 4 changed to Foscarnet due to bone marrow toxicity). All patients had kept viral loads (VL) at least for two weeks. Two patients had more than one episode of CMV reactivation. The details are shown in the table.

Genotypic CMV resistance of these patients was analyzed in the last sample of the last CMV episode at the Hospital Universitario Central de Asturias (Spain). UL97 gene was amplified by nested PCR with specific primers. The PCR products were excised from agarose gels and purified by Life Science Kit. Sequencing reactions were performed by chain-termination methods (Abi Prism 3100, Applied Biosystems).

RESULTS: Antiviral resistance was found in one patient (number 5) with the presence of A594V mutation that confers high-level resistance to Ganciclovir. The resistance appeared after three episodes of virus reactivation that required prolongated treatment of 28, 20 and 14 days with Ganciclovir. By not negativization of viral loads in the last two episodes, it changed to Foscarnet (during 14 days more in each episode) as maintenance therapy. The patient also suffered an episode of EBV reactivation treated with Rituximab. It is noteworthy that each CMV reactivation episodes have been associated with weakening of the hematopoietic graft.

CONCLUSION: A potential risk associated to antiviral use allows the emergence of resistant CMV. The study of CMV resistance in the routine of diagnostic virology laboratories should be recommended in the cases of therapeutic failure with persistent viral loads or multiple CMV reactivation episodes.

Patient	Age	Gender	Antibody CMV D/R	Prophylaxis	Type of transplant	Reactivation CMV episodes (days postransplant)		Average VL (copy/ml)	Nº days VL positive	Early treatment	Maintenance therapy
1	62	Male	+/+	Aciclovir	allo-SCT HLA-identical Related donor	2	+62	170	34	Foscarnet	No
							+132	1734	10	Foscarnet	Ganciclovir
2	39	Female	-/+	Aciclovir	allo-SCT HLA-different Unrelated donor	1	+62	2330	51	Valganciclovir	Foscarnet/ Valganciclovir
3	38	Male	+/-	Aciclovir	allo-SCT HLA-identical Unrelated donor	1	+45	10276	17	Ganciclovir	No
4	58	Male	+/-	Aciclovir	allo-SCT HLA-different Unrelated donor	1	+48	1143	28	Foscarnet	Foscarnet
5	54	Male	+/-	Aciclovir	allo-SCT HLA-different Unrelated donor	3	+ 62	312	28	Ganciclovir	Ganciclovir
							+94	470	30	Ganciclovir	Foscarnet
							+149	204	14	Ganciclovir	Foscarnet