patients undergoing allogeneic hematopoietic stem cell transplantation (alloSCT) is unclear. We performed a retrospective matched-control study of the outcomes of 31 patients with serological evidence of HC at the time they underwent alloSCT for a variety of hematological malignancies between 1998 and 2007 at the UTMDACC. For comparison, we identified 31 control patients with negative serology for HC, matched on age group, diagnosis, disease risk (poor vs. good), intensity of conditioning regimen (reduced vs. myeloablative) and donor type (referred to as *matched controls*). To confirm the validity of the matching procedure we extended the comparison to the 1800 seronegative patients (*all controls*) transplanted for the same diseases during the same period of time. Multivariate analysis took into account all variables used in our matching procedure.

The median age of the HC patients was 49 (range 26–72); 15 had AML/MDS, 6 CML/MPD, 6 non-Hodgkin lymphoma, 2 myeloma, 1 ALL and 1 Hodgkin lymphoma; 61% of had poor risk disease, 68% had related donors, and 68% received reduced intensity conditioning. These characteristics were identical to those of the matched control group. There were also no significant differences in baseline liver function: immediately prior to starting conditioning, only 7 patients in the HC group and 5 patients in the matched control group had an alanine transaminase (ALT) level greater than the upper limit of normal (ULN), but all less than 3×ULN (ranges 69–185 and 69–178 IU/L); only one patient in the HC group (versus none in the matched control) had a total bilirubin level above the ULN (1.2×ULN).

Median follow-up was 34 (range 3–53), 27 (4–74) and 29 months (1–108), respectively for HC, matched and all controls. Overall survival post-alloSCT was significantly inferior in the HC group, with a median OS of 3 versus 18 and 20 months in the control groups. The cumulative rate of disease progression and acute or chronic GVHD was comparable, but NRM was significantly increased in the HC group. Results were similar regardless of the control group used, validating our matching algorithm. In summary, serological evidence of HC virus infection at the time of alloSCT, even with normal or minimally abnormal liver function tests, is associated with worse survival after alloSCT, due to an increased rate of non-relapse deaths.

Patients with hepatitis C have worse overall survival and non-relapse mortality than controls after SCT

	Matched analysis			Multivariate analysis		
Outcome	HC (N = 31) vs. matched controls (N = 31), %	HR (95% CI)	P	HC (N = 31) vs. all controls (N = 1800), %	HR (95% CI)	P
OS:						
3 mo	58 vs. 87	3.6 (1.2–11.0)	0.03	58 vs. 87	3.9 (2.2–6.8)	<0.001
1 yr	29 vs. 56	2.4 (1.2–4.9)	0.01	29 vs. 56	3.1 (1.9–5.6)	<0.001
NRM:						
3 mo	29 vs. 13	2.5 (0.8–8.1)	0.1	29 vs. 10	3.6 (1.8–7.1)	<0.001
1 yr	43 vs. 24	2.9 (1.1–7.7)	0.03	43 vs. 23	3.3 (1.9–5.6)	<0.01

HC: hepatitis C, OS: overall survival, NRM: non-relapse mortality, HR: hazard ratio, CI: confidence interval.

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SERIAL VORICONAZOLE THERAPEUTIC DRUG MONITORING IN RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Trifilio, S.M.[1], Yarnold, P.R.[1], Pennick, G.[2], Pi, J.C.[1], Golf, M.[1], Fishman, M.[1], Masino, K.[1], Mehta, J.[1]. [1] Northwestern University, Chicago; [2] University of Texas at San Antonio, San Antonio.

Voriconazole is effective for prophylaxis and therapy of invasive fungal infections (IFI). It is metabolized by the CYP450 system 2C19, 2C9 and 3A4 isosenzymes. We have reported that significant interpatient variability exists in plasma voriconazole concentrations after allogeneic HSCT and that about 15% of patients have no detectable voriconazole in the plasma despite adequate dose (Trifilio et al. Cancer 2007;109:1532–1535). Low plasma levels have also been associated with decreased survival in patients with aspergillosis and increased breaktrough Candida glabrata infections (Trifilio et al. Bone Marrow Transplant 2007;40:451–456). Treatment or prophylaxis for IFIs after HSCT is prolonged, and changing conditions are likely to alter voriconazole pharmacokinetics which may predispose to treatment failure. We studied the relationship between the first and second voriconazole levels in 29 allogeneic HSCT recipients whose first plasma voriconazole level was adequate (>2 μg/mL). The first level was drawn 6 days after starting voriconazole (usually day +6 post-HSCT), and the second level was drawn at a variable time after the first (median 9 days; range 1–252 days). The majority of patients received the drug at the dose of 200 mg twice a day orally. The two levels were strongly correlated to each-other ($r = 0.72$; $p < 0.0001$), but not to the interval between the two ($p < 0.6$) or weight ($p < 0.49$). 10 patients had a level <2 μg/mL on the second measurement. Optimal discriminant analysis revealed that all 11 patients with an initial voriconazole level ≤4.6 μg/mL had a second level that was <2 μg/mL ($p < 0.02$). Neither the interval between the two levels ($p < 0.15$) or weight ($p < 0.75$) predicted whether a patient's second voriconazole level was <2 μg/mL. However, when the analysis was expanded to a total of 43 patients in whom the first level was ≥1 μg/mL, 10 of whom had a second level of <1 μg/mL, no factor could be found that could reliably predict for a second level of <1 μg/mL. These data suggest that serial plasma voriconazole levels can change in an unpredictable fashion over time after HSCT - sometimes decreasing to levels that may place the patient at risk for breakthrough IFIs. Patients who require prolonged voriconazole administration may benefit from ongoing therapeutic drug monitoring and dose adjustment.

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EFFICIENT INDUCTION AND ISOLATION OF A PRIMARY CMV-SPECIFIC CD8+ T CELL RESPONSE FROM CMV SERONEGATIVE DONORS FOR THE TREATMENT OF SERIOUS CMV-RELATED COMPLICATIONS IN CMV SEROPOSITIVE PATIENTS TRANSPLANTED WITH A CMV SERONEGATIVE DONOR

Jedema, I., van de Meent, M., van der Heiden, P.L.J., Marijt, E.W.A., Meij, P., Willemze, R., Falkenburg, J.H.F. Leiden University Medical Center, Leiden, Netherlands.

Cytomegalovirus (CMV) disease is a significant cause of morbidity and mortality after allogeneic stem cell transplantation (allo-SCT). Especially in CMV seropositive (CMV+) patients transplanted with a CMV- donor, a high incidence of CMV related mortality is seen. We recently demonstrated in a phase I/II clinical study the feasibility of selecting CMV-specific CD8+ memory T cells from CMV+ donors using the interferon-gamma (IFNg) capture assay and CliniMACS isolation after peptide stimulation of the CMV-specific donor T cells. We have illustrated the in-vivo potential of these T cells after adoptive transfer in 5 patients with persistent CMV reactivation despite seropositivity of the donor, resulting in clearance of the CMV load. However, no suitable method was available for the induction of primary immune responses against CMV for the treatment of persistent CMV reactivation in the high risk group of patients transplanted with a CMV- donor. In the current study we investigated the possibility to induce and isolate CMV-specific T cells from CMV- healthy donors by in-vitro priming and selection. We used as responder cells CD45RO- PBMC from HLA-A1, A2, A3, B7, or B8 positive CMV- donors (n = 13). By CD45RO depletion we removed the majority of regulatory T cells capable of inhibiting the initiation of the response. Naïve donor T cells were cocultured in the presence of IL-7 and IL-15 with mature monocyte-derived dendritic cells loaded with a cocktail containing 1μg of each relevant CMV pp65, pp50, or IE1 derived 9-mer peptide. At day 10, the responses were specifically restimulated with peptide loaded autologous PBMC. At day 20 CMV-specific CD8+ T cells were detected by specific tetramer or pentamer staining, and isolated by flowcytometric cell sorting or magnetic bead isolation, or further enriched by another restimulation, followed by isolation of CD137 or IFNg expressing T cells at day 21. In 13/13 CMV- donors CMV specific T cells could be detected at day 20 of the immune response in frequencies ranging from 0.01–0.4%. Functional CMV-specific T cells against all 3 major immunogenic CMV proteins pp65, pp50, and IE1 were isolated