Monitoring of varicella specific T-cell mediated immunity in pediatric allogenic hematopoietic stem cell transplant recipients

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INTRODUCTION

Varicella-zoster virus (VZV) infection is known to occur in 13-55% of patients within the first year after hematopoietic stem cell transplant (HSCT)[1].

VZV specific T-cell mediated immunity (CMI) is essential for prevention and control of VZV reactivation.

Allogenic HSCT recipients have reduced VZV-specific CMI. VZV-specific CMI following allogenic HSCT does not reconstitute in the absence of symptomatic VZV reactivation[2].

- In this study,
  - The reconstitution of VZV-specific CMI was assessed using IFN- γ ELISPOT as say before, 1 month and 3 months after HSCT.
  - The incidence of VZV disease in pediatric recipients under 19 years of age receiving allogenic HSCT at a single tertiary hospital was identified.
- The Extension study, which measures VZV-specific CMI before and after VZV vaccination at 24 months post-HSCT, is currently underway.

PATIENTS & METHODS

Patients

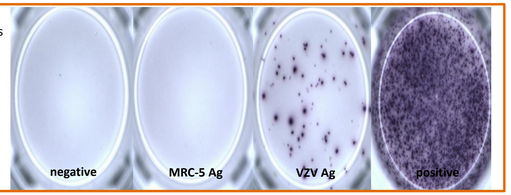
From April 2019 to February 2020, subjects aged ≤19 years who underwent allogenic HSCT with at least 1year of follow up at Asan Medical Center Children's Hospital were prospectively enrolled.

Evaluation of VZV specific CMI

Once before initiation of conditioning therapy, i.e., before HSCT and 1, 3 months after HSCT. Extension study, which measures VZV-specific CMI before and after VZV vacci nation at 24 months post-HSCT, is currently underway.

A peripheral venous blood sample up to 5 mL was collected from each patient for detecting VZV specific T cells producing IFN-γ by ELISPOT assay.

ELISPOT assay : detecting VZV- specific T cells producing IFN-γ



Reference

1) Arvin,A.M.(2000). Biol Blood Marrow Transplant, 6(3), 219-230.

2) Distler,E. (2007). Biol Blood Marrow Transplant, 14(12), 1417-1424.

RESULTS

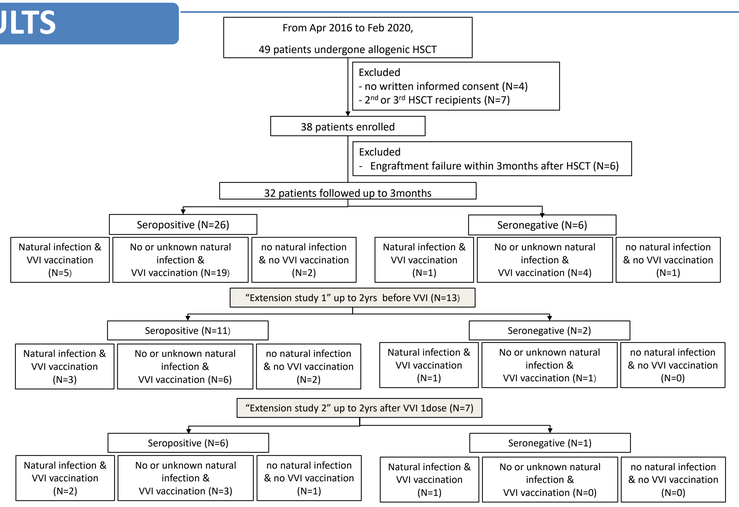


Figure 1. Follow diagram of study enrollment.

* VVI : Varicella virus vaccine live vaccine

Table2. Number(%) of patients by VZV-specific CMI by period.

VZV-specific CMI (SFC/2x10^{5}cells)	Pre-HSCT	1mo after HSCT	3mo after HSCT	2yr after HSCT	
				Before VVI	After VVI (1dose)
0	16(50)	13(40.6)	16(50)	3(23.1)	0(0.0)
1	3(9.4)	6(18.8)	5(15.6)	1(7.7)	1(14.3)
2	2(6.3)	5(15.6)	3(9.4)	1(7.7)	1(14.3)
3	2(6.3)	0(0.0)	1(3.1)	0(0.0)	0(0.0)
4	2(6.3)	2(6.3)	2(6.3)	1(7.7)	0(0.0)
5	1(3.1)	2(6.3)	1(3.1)	1(7.7)	1(14.3)
6	1(3.1)	0(0.0)	1(3.1)	2(15.4)	0(0.0)
7	1(3.1)	0(0.0)	0(0.0)	1(7.7)	1(14.3)
8	0(0.0)	0(0.0)	1(3.1)	2(15.4)	0(0.0)
9	0(0.0)	1(3.1)	0(0.0)	0(0.0)	1(14.3)
≥10	2(6.2)	1(3.1)	1(3.1)	1(7.7)	1(14.3)
≥50	1(3.1)	0(0.0)	0(0.0)	0(0.0)	1(14.3)
indeterminate	1(3.1)	2(6.2)	1(3.1)	0(0.0)	0(0.0)
Total number (%)	32(100.0)	32(100.0)	32(100.0)	13(100.0)	7(100.0)
	6(18.8%)	5(15.6%)	4 (12.5%)	7 (53.8%)	5 (71.4%)

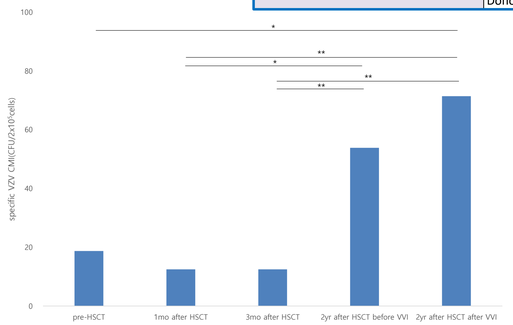


Figure 2. Proportion (%) of patients with VZV-specific CMI ≥5 SFC/2x10^{5}cells.

At 2 years after HSCT, the proportion of patients with VZV-specific CMI ≥5 increased significantly, but only 53.8% of all recipients.
(*P ≤ 0.05, ** P≤0.01)

Table 1. Demographic and characteristics of total 32 allogenic HSCT recipients

		No. of case	
Median age(y)(range)		11	(0-19)
Median follow up duration(months) (range)		17	(13-23)
Sex	Male	22	73.3%
	Female	10	31.3%
UnderlyingDz	Malignancy	18	56.3%
	AML,MDS	8	25.0%
	ALL	6	18.8%
	CML	2	6.3%
	SOLID	1	3.1%
	HLH	1	0.0%
	Non-malignancy	14	43.8%
	SAA	11	34.4%
	Others	3	9.4%
Donor type	Haploidentical	12	37.5%
	Non-hapoloidentical	20	62.5%
Conditioning	Myeloablative	11	34.4%
	Reduced intensity	21	65.6%
	ATG	32	100.0%
Varicella vaccination before HSCT	Yes	30	93.8%
	No	2	10.0%
History of chickenpox before HSCT	Yes	6	18.8%
	No	19	59.0%
	Unknown	7	21.9%
positive VZV Ab before HSCT	Recipient	26	81.3%
	Donor	11	34.4%

After HSCT		No. of case	
GvHD prophylaxis		32	100.0%
PTLD prophylaxis		12	37.5%
time to discontinuation of prophylactic Acyclovir	D30	2	6.3%
	D100	9	28.1%
	D365	21	65.6%
VZV disease		1	3.1%
CMV viremia		19	59.4%
CMV disease		2	6.3%
PTLD		3	9.4%
Acute GVHD		16	50.0%
Chronic GVHD		7	21.9%
Disease relapse		6	18.8%
Death		4	12.5%

*P ≤ 0.05, ** P≤0.01

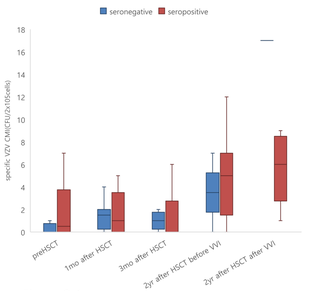


Figure 3-1

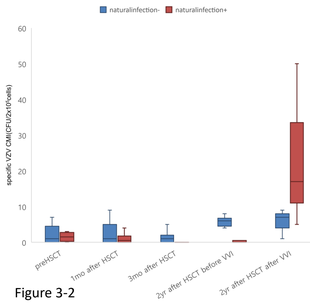


Figure 3-2

Figure 3. Change of VZV-specific CMI by period.

There was no difference in VZV-specific CMI according to VZV serostatus at HSCT (Fig3-1). In cases with natural VZV infections before HSCT, the VZV-specific CMI increased significantly after VZV vaccination (Fig3-2).

Conclusion

VZV-specific CMI decreased to very low levels early post-HSCT and the recovery of CMI ≥ 5 SFC/ 2.0×10^5 cells was observed only in 12.5% of recipients at 3 months following HSCT. Only one recipient (3.1%) experienced VZV reactivation within 2 years after HSCT. VZV vaccination at 2 years post-HSCT boosted VZV-specific T cells especially in the seropositive recipients.

More long-term large-scale multicenter study is mandatory to supplement these parts.