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Norovirus Infection in Cancer Patients Undergoing Chimeric Antigen Receptor T-cell Immunotherapy (CAR-T)

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BACKGROUND

CAR-T is used to treat certain refractory hematological malignancies. B-cell aplasia and immunosuppression used to treat CAR-T side effects increase infection risk.

Little data are available describing Norovirus (NoV) infections in CAR-T recipients. We describe the demographics, clinical characteristics, treatments and complications of 9 CAR-T patients that developed NoV diarrhea.

INTRODUCTION

- Noroviruses are small, non-enveloped RNA viruses that belong to the *Caliciviridae* family.
- NoV is the leading cause of virus-associated diarrhea in the immunocompromised population and can cause a protracted course of illness with complications of malnutrition, dehydration and altered mucosal barrier.
- NoVs are divided into 10 genogroups of which 5 genogroups (GI, GII and GIV, GVIII and GIX) are associated with disease in humans.
- Genogroup II, genotype 4 (GII.4) is the most common cause of infections worldwide. While NoV epidemiology is complex, strain diversity is greater in immunocompromised patients compared to immunocompetent hosts.

METHODS

We reviewed the medical records of 134 patients with NoV diarrhea (identified by nucleic acid amplification test) between 2016-2019. Of these patients, nine received CAR-T prior to developing NoV diarrhea.

For molecular detection of NoV, RNA was extracted from a 1:200 dilution of stool samples by heat release (Schwab et al.) and real-time PCR was performed using the primers/probes NIFG1F/ NV1LCR and NIFG1P for detecting genogroup I viruses and NIFG2F/ COG2R and QNIFS for detecting genogroup II strains (Miura et al.)

Positive samples were genotyped by sequencing a 570 bp region of the NoV genome that was amplified using the primers MON 431 and G2SKR (Koo et al). Capsid and polymerase genotypes (P type) were determined for each sample.

Breakdown of malignancies

Type of Malignancy	n(%)
Diffuse large B cell lymphoma	3 (33)
Follicular lymphoma	1 (11)
B cell Acute lymphoblastic Leukemia	2 (22)
T cell Acute lymphoblastic leukemia	1 (11)
Chronic Lymphocytic leukemia	1 (11)
Metastatic Sarcoma	1 (11)

Demographics	n(%)
Age	
Median (range)(y)	49 (13-69)
Gender	
Male	5 (56)
Race & Ethnicity	
Caucasian	6 (67)
Hispanic Ethnicity	3 (33)

RESULTS

Table 1: Clinical and laboratory characteristics

Clinical characteristics	n(%)
Chemotherapy in prior 3 months	6 (67)
Prior HSCT	6 (67)
Prior checkpoint inhibitor therapy	1 (11)
Lab findings	
Lymphopenia<1000/mm^3	6 (67)
ANC<500/mm^3	4 (44)
Albumin, median(range, mg/dl)	3.5 (2.7-4.1)
IgG<400mg/dl,receiving IVIg	8 (89)*

*IgG levels not documented for the 9th patient

Table 2: CAR-T specific characteristics

Car T related factors	n(%)
Cyclophosphamide, Fludarabine conditioning	8 (89)
Type of CAR-T	
Anti-CD19	6 (67)
CD8+ Cytotoxic T cell	1 (11)
Cord blood NK cells	2 (22)
CAR-T toxicities**	
Cytokine release syndrome	5 (56)
CAR-T related encephalopathy syndrome	1 (11)
Immune mediated Colitis	1 (11)

**2 patients received *IL-6* antagonist therapy, and 1 patient received high dose steroids

Table 3: NoV Genotypes

NoV genotypes	n(%)	No of samples	Cycle threshold Ct
GII.2(P16)	2(22)	Patient #1- 1 sample	24.5
		Patient#2-5 samples	25.74, 22.28, 24.34 23.63, 25.88
GII.4(P31)	1(11)	3	36.9, 28.12, 29.42
GII.6(P7)	1(11)	1	21.4
GII.12(P16)	1(11)	1	28.0
GII.4Sydney(P16)	1(11)	3	32.47, 30.69, 28.0

Three patients had diarrhea lasting >14 days, they had samples collected over time; NoV shedding lasted 81-546 days. The median diarrhea duration in the other 6 patients was 4 days

- All patients (9) had diarrhea. Other GI complaints included abdominal pain (3), nausea (4), and vomiting (3).
- For NoV treatment, three patients received oral immunoglobulin, and 8 received Nitazoxanide.
- Complications included development of concomitant GI-GVHD(5), ileus (2), need for TPN (3), renal failure requiring dialysis (2), ICU stay (3), and death (2).

CONCLUSIONS

As NoV can be shed for prolonged periods of time, it will be important to determine if NoV is associated with malnutrition, contributes to enteric damage when concomitant chemotherapy is administered and serves as a source for nosocomial spread. Given the high sensitivity of the various multiplex panels in detecting various pathogens, it becomes difficult to attribute causality of clinical condition to NoV alone, when multiple pathogens or various overlapping conditions are present simultaneously.

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