VOL. 3, NO. 6, 2023
ISSN 2772-3747

Letters

RESEARCH LETTER

Impact of Cytokine Release Syndrome on Cardiac Function After Chimeric Antigen Receptor-T Cell Therapy

As chimeric antigen receptor-T cell (CAR-T) therapy by tisagenlecleucel gains advantages in the management of diffuse large B cell lymphoma (DLBCL), accumulating evidence shows that cytokine release syndrome (CRS) frequently follows CAR-T therapy with adverse cardiovascular manifestations.[1] Although tocilizumab was mostly used on day 5 in a previous study,[1] early and aggressive administration is currently recommended because CRS severity peaks by day 3.[2] However, the impact of CRS severity on cardiac function and on the prognosis of DLBCL patients in the era of aggressive use of tocilizumab remains unclear.

Thirty consecutive DLBCL patients without prior cardiovascular disease history who underwent CAR-T therapy were enrolled. CRS is divided into 5 grades according to the degree of fever, hypotension, and hypoxia according to the consensus for the CRS grading system.[3] Patients were classified into low-CRS (grade <2) and high-CRS (grade ≥ 2) groups. The sequential changes in biomarkers and echocardiography were examined. Echocardiography was performed at baseline and days 7, 14, and 28 by the sonographers blinded to the clinical information, and blood samples were collected at baseline and days 3, 7, 14, and 28 after CAR-T therapy. The study protocol was approved by the institutional ethical committee of Hyogo Medical University.

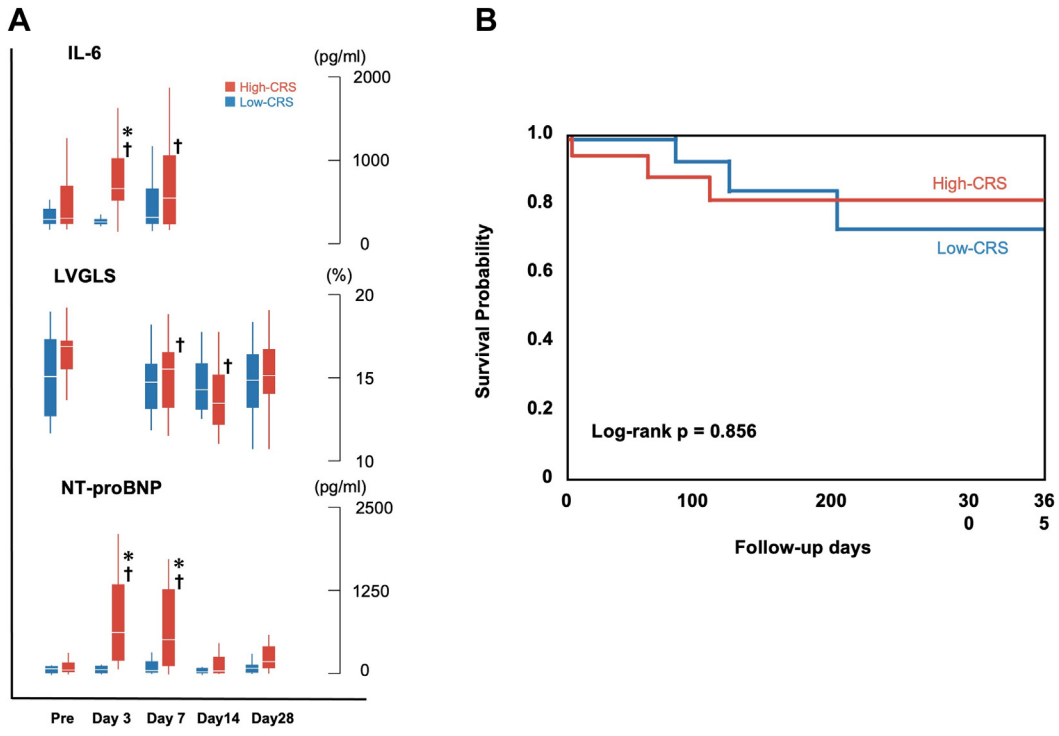
The average age was 59.6 years, and 9 (30%) were women. The number of patients in the low- and high-CRS groups was 13 and 17, respectively, of whom 6 and 12 were diagnosed by board-certified hematologists as indicative of tocilizumab. The median time point of tocilizumab administration was day 2 (IQR: 1-4 days). At baseline, there were no significant differences in biomarkers or echocardiography between the 2 groups (**Figure 1A**). The high-CRS group showed significantly higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels than the low-CRS group on day 3 (623 pg/mL [IQR: 228-1,245 pg/mL] vs 90 pg/mL [IQR: 48-134 pg/mL]; $P < 0.001$) and day 7 (520 pg/mL [IQR: 169-1,194 pg/mL] vs 75 pg/mL [IQR: 45-193 pg/mL]; $P = 0.003$), whereas troponin T levels did not show differences. Four cases required inotropic support during CRS, but the reanalysis after discarding them did not impact these results. The levels of interleukin (IL)-6 and IL-1β on day 3 were significantly higher in the high-CRS group (567.3 pg/mL [IQR: 438.1-906.6 pg/mL] vs 155.5 pg/mL [IQR: 126.3-182.5 pg/mL] and 17.3 pg/mL [IQR: 11.8-23.1 pg/mL] vs 11.0 pg/mL [IQR: 10.5-12.0 pg/mL], respectively; all $P < 0.05$). On day 7, the level of IL-6 peaked out, whereas the level of IL-1β increased further from day 3. Notably, the NT-proBNP level on day 3 correlated with the IL-6 level ($r = 0.644$, $P < 0.001$) and IL-1β level ($r = 0.628$, $P < 0.001$).

Echocardiography demonstrated that left ventricular global longitudinal strain significantly decreased compared with baseline on days 7 and 14 (19.1% [IQR: 17.6%-19.5%] vs 17.4% [IQR: 14.7%-18.5%] and vs 14.8% [IQR: 13.8%-16.5%]; all $P < 0.05$) and recovered toward baseline on day 28 in the high-CRS group. However, there was no significant change in left ventricular ejection fraction in either group during the study period. Despite these changes in the acute phase, there were no major cardiac events, and the long-term mortality was comparable between the 2 groups (**Figure 1B**).

To our best knowledge, this is the first prospective study enrolling DLBCL patients treated with CAR-T therapy to investigate the relationship between CRS severity and cardiac biomarkers, cytokines, and echocardiograms over time. In our study, decreased left ventricular global longitudinal strain and increased NT-proBNP on days 3 and 7 were observed in the high-CRS group, but they improved by day 28. These changes were transient and did not result in overt cardiovascular disorders or poor mortality.

As limitations, this was a small-sized single-center study. Also, the impact of an on-target/off-tumor effect as well as an off-target effect was not examined in this study and needs further investigation.

FIGURE 1 Impact of CRS on Cardiovascular Manifestations After Chimeric Antigen Receptor T Cell Therapy



(A) Biological parameters in acute phase. (B) Prognosis in chronic phase. *Low-cytokine release syndrome (CRS) group vs high-CRS group, $P < 0.05$. †vs pre, $P < 0.05$. IL = interleukin; LVGLS = left ventricular global longitudinal strain; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

This study highlights a lower prevalence of severe adverse cardiovascular manifestations after CRS that require intensive cardiovascular care and comparable long-term mortality between those who had the low and high CRS after CAR-T therapy under an aggressive tocilizumab administration policy in the current real-world practice.

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https://doi.org/10.1016/j.jacasi.2023.08.010

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

JACC: ASIA, VOL. 3, NO. 6, 2023
DECEMBER 2023:944–946

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