Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2024, Volume 4, Issue 2, Page No: 1-4

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Delayed Hematologic Toxicities Following Axicabtagene Ciloleucel and Tisagenlecleucel CAR-T Cell Therapy: A Retrospective Analysis of Lymphocytopenia, Neutropenia, and Thrombocytopenia

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Received: 10 May 2024; **Revised:** 03 August 2024; **Accepted:** 06 August 2024

ABSTRACT

This study provides a 2024 update on survival outcomes and the frequency of hematologic complications, specifically lymphocytopenia, neutropenia, and thrombocytopenia, in patients treated with axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) CAR-T cell therapies. The study examined 56 patients diagnosed with diffuse large B-cell lymphoma who underwent CAR-T cell therapy from 2019 to March 2024. Among them, 34 patients received axi-cel (group A), and 22 patients were treated with tisa-cel (group B). The cumulative survival rate was calculated using the Kaplan-Meier method, while the occurrence of delayed cytopenias (beyond 60 days post-treatment) was assessed through follow-up blood tests, with grading based on the National Cancer Institute's Common Terminology Criteria for Adverse Events. The study cohort (n = 56) had a mean age of 55 years (range 46–64 years), a mean weight of 75 kg (range 52–98 kg), and a mean height of 161 cm (range 145–178 cm). Women comprised 49% of the group. The cumulative survival rates were 65.5% for axi-cel and 56.5% for tisa-cel, with incidences of lymphopenia, neutropenia, and thrombocytopenia recorded at 21.4%, 5.3%, and 12.5%, respectively. The mean disease-free survival was 19 months (SD = 14), and the mean survival time after treatment was 10 months (SD = 9). This analysis suggests that late-onset cytopenias following CAR-T cell therapy are relatively rare, though they may result from a variety of underlying mechanisms in vulnerable patients.

Keywords: Axicabtagene ciloleucel, Tisagenlecleucel, CAR-T therapy, Hematologic toxicity, Cytopenia

How to Cite This Article: Bona C, Lozano R. Delayed Hematologic Toxicities Following Axicabtagene Ciloleucel and Tisagenlecleucel CAR-T Cell Therapy: A Retrospective Analysis of Lymphocytopenia, Neutropenia, and Thrombocytopenia. Asian J Curr Res Clin Cancer. 2024;4(2):1-4. https://doi.org/10.51847/uN2cjdmOP8

Introduction

CAR-T cell therapy targeting CD19 has emerged as a groundbreaking approach in the treatment of diffuse large B-cell lymphoma (DLBCL), providing new treatment options for patients with few alternatives [1]. However, the side effects associated with this therapy, particularly cytopenias, are garnering more attention due to their potential impact on both morbidity and non-relapse mortality [2, 3].

Assessing cumulative survival rates in real-world scenarios and understanding the occurrence of late-onset cytopenias, defined as those developing more than 60 days after treatment, continues to be a complex challenge in clinical practice [4, 5].

Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), both of which are approved in Spain, may differ in their profiles for causing various hematologic toxicities. It is essential to evaluate severe cytopenias (grade ≥ 4) and their influence on survival to enhance the effectiveness of CAR-T therapy and improve patient outcomes [6, 7].

This study aims to offer a 2024 update on cumulative survival and examine the incidence of delayed lymphocytopenia, neutropenia, and thrombocytopenia in patients treated with axi-cel and tisa-cel CAR-T therapies beyond 60 days post-treatment [8, 9].

Materials and Methods

This study involved a cohort of consecutive patients from various CAR-T treatment centers in Aragon, Spain, who underwent adoptive CAR-T cell therapy between 2019 and March 2024. A total of 56 patients diagnosed with diffuse large B-cell lymphoma (DLBCL), treated with CD19-targeted CAR-T therapy as their third-line treatment, were included in the analysis. These patients were divided into two groups: group A consisted of 34 patients who received axicabtagene ciloleucel (Yescarta®), while group B included 22 patients treated with tisagenlecleucel (Kymriah®).

The study aimed to estimate the cumulative survival (CS) using the Kaplan-Meier (KM) method, and to assess the development of late-onset cytopenias, specifically lymphocytopenia, neutropenia, and thrombocytopenia, occurring after day 60 post-treatment [10, 11]. Blood samples were collected according to protocol, with the most current available data being analyzed. The cytopenias were classified based on their severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [12]. Severe thrombocytopenia was defined as a platelet count of less than 50 G/L, profound neutropenia as a neutrophil count under 500/µL, severe lymphopenia as a lymphocyte count between 200 and 499/µL, and very severe lymphopenia as a lymphocyte count below 200/µL [13, 14].

Data for this analysis were obtained from the hospitals' laboratory records, which were supported by the electronic prescription systems. Survival estimates were generated using the Kaplan-Meier method, which accounts for patients censored before the event of interest. The cumulative survival rate over 50 months was estimated from the time of CAR-T infusion. To compare survival distributions between group A and group B, the log-rank test was utilized.

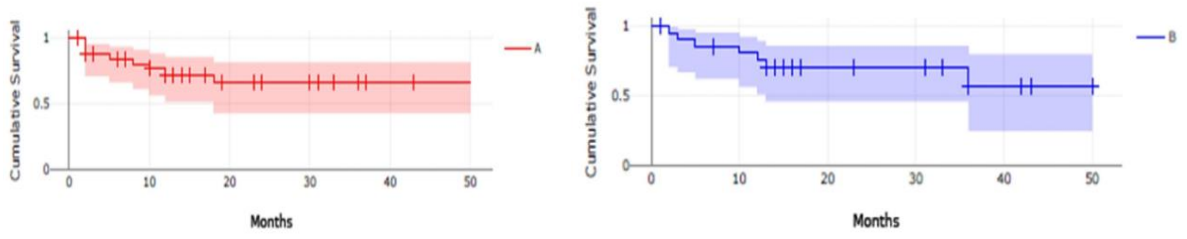
The study also focused on calculating the proportion of patients experiencing severe (grade ≥ 4) cytopenias, including lymphocytopenia, neutropenia, and thrombocytopenia, using the latest available hematological results. These proportions were compared between the two groups using Fisher's exact test.

Given that this was a retrospective study based on secondary data from Spanish public hospitals, ethical approval was not required. However, the research adhered to the ethical principles outlined in the 1975 Declaration of Helsinki, as revised in 2013.

Results and Discussion

The study included 56 patients, with an average follow-up time of 16 months (SD = 13). The cohort was composed of 49% females, with a mean age of 55 years (SD = 9), average weight of 75 kg (SD = 23), and mean height of 161 cm (SD = 18). Of the patients, 34 (50.7%) were treated with axicabtagene ciloleucel (group A), and 22 (32.8%) received tisagenlecleucel (group B) for diffuse large B-cell lymphoma (DLBCL).

For the group treated with axi-cel (group A), the estimated cumulative survival (CS) rate was 65.5%, with 9 events and 25 censored data points (n = 34; survival rate = 0.6554, SD = 0.09986, 95% CI = 0.4246-0.8118). Meanwhile, the CS rate for those treated with tisa-cel (group B) was 56.5%, with 7 events and 15 censored data points (n = 22; survival rate = 0.5647, SD = 0.15, 95% CI = 0.2415-0.7947) **(Figure 1)**.



a) b)

Figure 1. Cumulative survival Kaplan-Meier curves; a) survival function (S_t)–with confidence interval, and b) survival function (St)–with confidence interval

The cumulative survival data are displayed through Kaplan-Meier curves for two groups: 34 patients treated with axicabtagene ciloleucel (Yescarta®) in panel A, and 22 patients who received tisagenlecleucel (Kymriah®) in panel B. Shaded regions represent the 95% confidence intervals. The number of patients at risk is shown at one-month intervals, with tick marks denoting censored data points.

A statistical comparison using the log-rank test indicated no significant difference in survival between the two treatment groups (P-value = 0.996191; P ($x \leq \chi^2$) = 0.00380938).

Out of the cohort, 12 patients (21.4%) developed severe lymphocytopenia, including 7 (58.3%) in the axi-cel group and 5 (41.7%) in the tisa-cel group. Among these, 7 cases (58.3%) were categorized as very severe lymphopenia, and 9 of these patients (75%) died. Furthermore, 3 patients (5.3%) experienced profound neutropenia, all of whom were in the tisa-cel group, and all of these patients passed away. Additionally, 7 patients (12.5%) experienced thrombocytopenia: 5 (8.9%) in the axi-cel group, of which 4 (80%) died.

The average disease-free survival duration until March 2024 was 19 months (SD = 14), while the average time to death was 10 months (SD = 9).

In terms of toxicity, the NCI grading system indicated that life-threatening cytopenias (grade ≥ 4) affected 21.4% of patients for lymphocytopenia, 5.3% for neutropenia, and 12.5% for thrombocytopenia. Although there were differences in cytopenia occurrence and cumulative survival between the two groups, these differences were not statistically significant.

Our findings on cumulative survival for axi-cel (65.5%) and tisa-cel (56.5%) closely mirror the data in existing literature, where survival rates typically range from 67% to 74% for these treatments [15, 16].

Late-onset cytopenias, which occur after CAR-T infusion, are not entirely understood. They may be influenced by factors such as prior chemotherapy, radiation therapy, bone marrow infiltration, the CAR construct design, and the CAR-T infusion itself. These variables may contribute to persistent bone marrow suppression and chronic cytopenia [17, 18]. Moreover, the variations in cytokine release seen across different CAR-T therapies could be related to the CAR construct's design, which may impact the development of cytopenias post-treatment [19]. Given that CD19 CAR-T cells target both CD19 and CD45 on the B cells, differences in how these markers are expressed could also play a role in the immune response and potential side effects.

Given the findings above, it is plausible that cross-reactivity occurs between B cells expressing both CD19 and CD45, the intended targets of axi-cel and tisa-cel, and other lymphoid cells that also express CD45 (such as T cells, neutrophils, and platelets). This interaction could potentially trigger the formation of autoantigens associated with CD45 or other shared markers, leading to the development of various cytopenias.

In conclusion, while CAR-T cell therapies have shown substantial therapeutic success, particularly in treating certain cancers, concerns over their side effects persist. Recent studies have raised the possibility that vector integration could result in the expression of CD45-related antigens, potentially leading to immune cross-reactivity between cells that express both CD19 and CD45 or other common markers found in myeloid and lymphoid cells. This could contribute to the development of pancytopenia in some patients [16].

Several limitations to this study should be noted. First, the retrospective nature of the study means that the data may not fully capture all relevant outcomes, particularly late-grade cytopenias (those occurring beyond 60 days after treatment). A significant number of patients did not have available follow-up data after this point due to loss to follow-up or incomplete records. Moreover, while this research was conducted in a real-world setting, there was considerable variability in patient characteristics, treatment protocols, and approaches to managing side effects. Furthermore, factors such as the specific CAR-T product used, the type of malignancy treated, and other potential influences on the occurrence of late cytopenias and survival outcomes were not explored due to the small cohort size.

Conclusion

The findings of this study suggest that while the development of late-onset cytopenias after CAR-T cell therapy is uncommon, such events may occur in certain patients due to various factors. The mechanisms behind these late effects require further investigation to improve patient management and treatment outcomes.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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