HSD10

The hospital care pathway of patients treated by axi-cel and tisa-cel between 2018 and 2021 in France: a national study based on the comprehensive inpatient stays database

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Background

- Since 2018, treatment with CAR T-cell (genetically engineered T cells to specifically target and destroy tumor cells) has rapidly shown promising therapeutic results and is now the standard of care in patients treated for certain types of non-Hodgkin lymphoma.[1,2] Axi-cel and tisa-cel treatments were on the market as part of temporary authorizations for use (ATU) as early as 2018, before entering common law in July 2019 and December 2019, respectively.
  - Axi-cel[3] is indicated for the treatment of adult patients with refractory or relapsed diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after at least two lines of systemic therapy.
  - Tisa-cel[4] is indicated for refractory, post-transplant relapsed or second or later relapsed B-cell lymphoma, adults with relapsed or refractory DLBCL after the second or later line of systemic therapy, and adults with relapsed or refractory follicular lymphoma (FL) after the second or later line of systemic therapy.
- The introduction of this therapeutic innovation and the gradual opening of qualified centers has changed the patient care pathway. The organization before and after the administration of a CAR T-cell is complex (leukapheresis, bridging chemotherapy, lymphodepletion, management of specific toxicities, long-term follow-up post-administration, etc.). In addition, the recommendations of the SFGM-TC* is 10 days of hospitalization after CAR T-cell administration (if the patient is less than one hour from the qualified centers), while the EHA** recommends a duration of 14 days.[7,8] No study conducted in France describing the stay of patients treated with CAR T-cell has been identified.

**SFGM-TC French Society of Marrow Transplantation and Cell Therapies*

***EHA European Hematology Association*

Objective

- The objective of this study was to describe the pathway of the patients treated by axi-cel and tisa-cel from 2018 to 2021, and to study the variables influencing the pathways.

Methods

Study design and data sources

- A retrospective cohort of patients hospitalized for axi-cel or tisa-cel administration between January 1, 2018, and December 31, 2021, was constituted from the comprehensive databases of hospital stays in France (PMSI).
- The hospital stays and healthcare consumption of the patients in the cohort were extracted from the 4 years before and up to one year after CAR T-cell administration.

Eligibility criteria

- Patients with a full hospital stay for axi-cel and tisa-cel administration over the study period were included.
- Patients who were under 18 years old and/or treated for acute lymphoblastic leukemia were excluded.

Analysis methodology

- A descriptive analysis of patients' characteristics, CAR T-cell centers and CAR T-cell treatment-related stays was performed. Diseases and comorbidities were investigated within 4 years prior dosing.
- The patient's journey was divided in five periods (Figure 1), three before the index date, the pre-leukapheresis and the bridging therapy periods followed by the lymphodepletion window, and two after the index date, the post-CAR-T short-term and post-CAR-T long-term periods (Table 1).
- The centers were classified in three levels of experience, according to the average number of patients treated by month in 2021:
  - High experience (≥2 patients/month)
  - Intermediate experience (<2 patients/month)
  - Low experience (<1 patient/month)
- The characteristics of the CAR T-cell stay were analyzed according to the type of CAR T-cell administered, axi-cel or tisa-cel, and according to the centers' level of experience.
- The distances between patients' home and CAR T-cell centers were defined with the patients' municipality of residence and the address of hospitals. Distances were valued from defined car trips using the API[9] google maps tool.

Figure 1. The patient's journey's periods

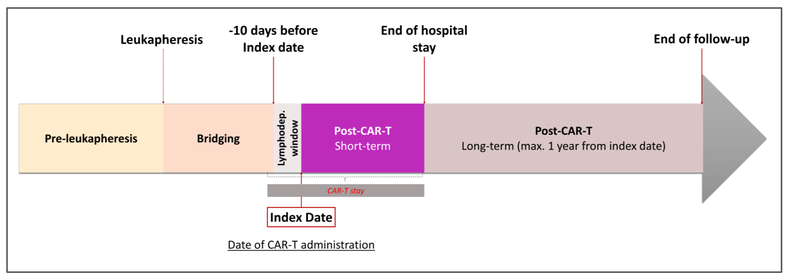


Table 1. Periods used to describe the patient's journey

Patient's journey periods	Definition	Population analyzed
Pre-leukapheresis	This period starts 4 months before the index date and ends on the date of leukapheresis	Restricted to patients with leukapheresis date available
Bridging therapy	This period starts on the date of leukapheresis and ends eleven days before the index date	Restricted to patients with leukapheresis date available
Lymphodepletion window[a]	This period starts ten days before the index date and ends on the day before the index date	All patients
Post-CAR-T short term	This period starts on the index date and ends on the date of hospital discharge	All patients
Post-CAR-T long term	This period starts one day after the date of hospital discharge and ends up until 12 months after the index date	Patients alive

[a]*The term "window" means that the period is defined ex-ante (duration of 10 days), not by the onset of an event.*

Predictors of the patient's journey

- Four indicators were used to identify the factors that predict the patient's journey : the duration and setting of the bridging therapy, the length of the patient's stay for CAR T-cell therapy and the management of the post-infusion stay.
  - In a first step, the adjustment variables were chosen among the patients' characteristics, centers' characteristics, type of CAR T-cell infused, and coverage method. These variables were selected for (i) either on their statistical significance in the bivariate analysis ($p<0.2$), (ii) or on their clinical interest. Although being tested, the region of the center(s) and the region of the patients were not considered for multivariate analysis, due to the high number of categories and the low number of patients in each category.
  - In a second step, multivariate analyses were carried out to identify the predictors of the patient's journey. Two types of mixed-effect regression models were used: (i) linear for duration of the bridging therapy and length of the CAR T-cell stay, (ii) logistic for the setting of the bridging therapy and for the post-infusion stay management. The data driving the patient's journey are organized in two levels: centers and individuals (the patients being statistically "nested" within the center). The experience of the CAR T-cell center was considered as a random effect
  - Since the experience of the center was considered as a random effect, the significance of the adjusted effect was not available.

Results

Population

In France, between 01/01/2018 and 31/12/2021, 901 patients received treatment with CAR T-cell and were included in the study. The proportion of patients treated with axi-cel was 60.8% (n=548) and 39.2% for patients treated with tisa-cel (n=353). The number of acredited CAR T-cell centers went from 2 in 2018 to 26 in 2021.

- The number of patients treated with CAR T-cell increased by +48% respectively between 2019 and 2020, then by +34% between 2020 and 2021.
- The average distance patients traveled to the center decreased from 170 km (ranging from 2 to 869 km) to 117 km (ranging from 1 to 765 km) between 2018 and 2021.

Center characteristics

- The centers were classified in three levels of experience:
  - High experience (≥2 patients/month): 6 centers, 59.9% of all patients.
  - Intermediate experience (<2 patients/month): 10 centers, 34.2% of all patients.
  - Low experience (<1 patient/month): 10 centers, 5.9% of all patients.

Table 2. Characteristics of patients treated with CAR T-cell

Center Experience	Low n = 56	Inter. n = 291	High n = 554	Total n = 901
Average age (in years)	57.1±15.7	53.5±20.4	55.7±17.3	55.0±18.3
Male gender	66.1%	62.2%	60.3%	61.3%
Charlson Comorbidity Score	3.7±2.6	3.9±2.7	3.2±2.1	3.5±2.4
Diagnosis				
Diffuse large B-cell lymphoma	66,1%	80.1%	70.6%	73.4%
Transformed follicular lymphoma	23.2%	14.8%	21.8%	19.6%
Primary mediastinal large B-cell lymphoma	1.8%	4.1%	3.8%	3.8%
Transformed marginal zone lymphoma	7.1%	0.7%	2.5%	2.2%
Indeterminate B-cell lymphoma	1.8%	0.3%	1.3%	1.0%
Time from first hospitalization to CAR T-cell administration (months)	15.4±12.7	15.0±12.2	15.2±11.8	15.1±11.3
History of hematopoietic stem cell transplantation	30.7%	25,1%	24,4%	25,0%

Results are presented as percentage or mean ± standard deviation

Characteristics of the CAR T-cell infusion stay

The mean length of stay (LOS) for CAR T-cell administration was approximately 25 days with a time from dosing to the end of stay of nearly 18 days (Table 3). It varied depending on the mode of discharge (24.1 days in the case of a return home, 26.9 days in the case of SSR transfers, 21.8 days in the case of transfer to another MCO service and 45 days in the case of death).

Table 3. Characteristics of the CAR T-cell infusion stay according to the level of experience

Center Experience	Low n = 56	Intermediate n = 291	High n = 554	Total n = 901
Length of stay (days) [a]				
Overall	28.9±14.8	27.6±15.8	23.1±11.1	24.9±13.2
Admission to infusion	7.6±3.8	7.5±6.8	6.5±3.7	6.9±5.0
Infusion to discharge	21.3±14.1	20.1±12.2	16.7±10.4	18.1±11.4
Length of stay accounting for previous stays (days) [a,b]	30.1±14.7	29.1±16.5	26.7±15.4	27.7±15.7
Proportion of patients with ICU admission	64.3%	5.5%	26.9%	22.3%
Mode of discharge				
Home	62.5%	71.1%	78.0%	74.8%
Mutation/transfer	30.4%	25.0%	18.6%	21.4%
Death	7.1%	3.8%	3.4%	3.8%

[a] *Results are presented as mean ± standard deviation;* [b] *This length of stay includes all stays preceding the index stay without hospital discharge in between (i.e., transfer or mutation with 0 day between the two stays)*

Table 4. CAR T-cells journey period length according to the level of experience (days)

Center Experience	Low n = 56	Intermediate n = 291	High n = 554	Total n = 901
Bridging therapy				
Number of patients	n = 41	n = 192	n = 392	n=625
Period length	46.9 ±23.0	39.5 ±18.0	34.1 ±12.8	36.6±15.8
Lymphodepletion window				
Number of patients	n = 56	n = 291	n = 554	n = 901
Period length	10.0±0	10.0±0	10.0±0	10.0±0
Leukapheresis to CAR T-cell administration*				
Number of patients	n = 41	n = 192	n = 392	n=625
Period length	56.9 ±23.0	49.5 ±18.0	44.1 ±12.8	46.6± 15.8
Post-CAR T short term				
Number of patients	n = 56	n = 291	n = 554	n = 901
Period length	21.3 ±14.1	20.1 ±12.2	16.7 ±10.4	18.1 ±11.4
Post-CAR T long term				
Number of patients	n = 51	n = 277	n = 527	n = 901
Period length	124.8 ±100.1	207.3 ±123.7	228.7 ±125.9	215.6±126.1

*Results are presented as mean ± standard deviation. * The duration between leukapheresis and CAR-T cell administration is the duration bridging therapy plus 10 days of Lymphodepletion window.*

Predictors of the patient's journey

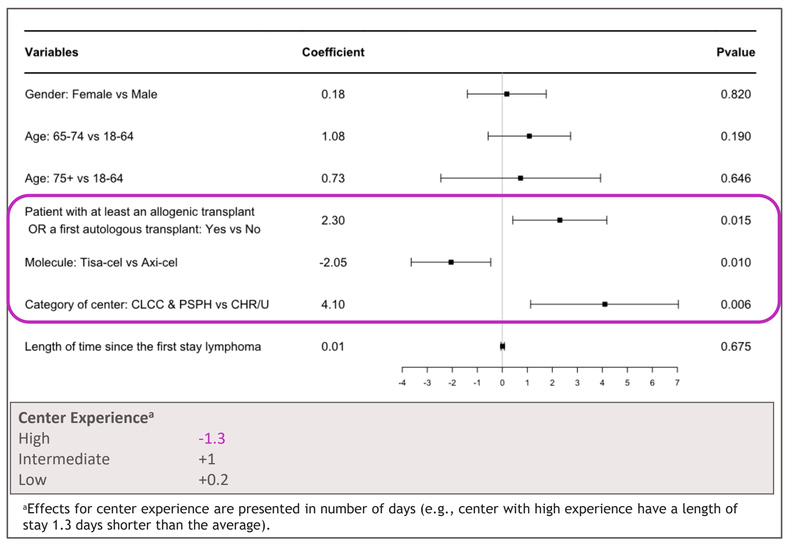
- **Duration of the bridging therapy**
  - **The duration of the bridging therapy decreased significantly ($p<0.0001$) with the level of the centers' experience, the mean difference is 12,8 days between high and low experience.**
  - Non-significant trends were observed for the patient's gender and age, the duration of the bridging therapy being shorter for female and older patients, for patients treated with axi-cel and in university centers (CHU).
  - **After running the multivariate analysis, the experience of the center was the sole determinant of the duration of the bridging therapy**, with shorter duration as the experience increases (-6.5 days for each level of experience, on average).

- **Setting of the bridging therapy**
  - **A significant effect can be observed for three variables. The patients were more likely to attend another center (not exclusively the CAR T center) for the bridging therapy if they were younger, treated in a center with a high experience, and in a university center.**
    - **Age.** The patients aged 18-64 represented 62.3% of the patients attending another center, whereas this proportion was 51.7% for the patients exclusively attending the CAR T-cell Center.
    - **Center's experience**. On average, the patients had a 43% probability to attend another center. A total of 77.9% of patients who attended another center were hospitalized in a center with high experience while only 47.1% when exclusively attending the CAR T-cell Center.
    - **University center.** Similarly, 96% of the patients attending another center were treated in a university center (versus 83.8% for patients attending exclusively the CAR T-cell center).
  - A non-significant trend was observed for the gender, women being more prone to attend another center than men.
  - **After running the multivariate analysis, the experience of the center was the sole determinant of the bridging therapy duration**, with higher probability to attend another center for the bridging therapy when centers' experience was high: -31,8%, -26,8%, and +104,9% probability for low, intermediate and high experience, respectively. A trend towards a higher probability to exclusively attend the CAR T-cell center for the bridging therapy was observed for older patients, men and patients treated in university centers.

- **Length of the CAR T-cell stay**
  - **The stay was shorter for patients without a history of transplant, treated with tisa-cel, in a center with high experience and/or a university center.**
    - **Transplant.** Patients who had previously undergone a transplant had an average stay of 19.7 days, whereas those who never had undergone one had an average stay of 17.6 days.
    - **Center's experience.** Patients treated in centers with low experience had an average stay of 21.3 days, while those treated in centers with intermediate or high experience had average stays of 20.1 and 16.7 days, respectively.
    - **Molecule.** Patients treated with tisa-cel had a significantly shorter stay duration (16.9 days) than those treated with axi-cel (18.9 days).
    - **University center.** Hospitalization in a university center was associated with an average stay of 17.6 days versus 23.2 days for non-university hospitals (CLCC* and PSPH**).
  - **Three of the predictors tested in the multivariate analysis were associated with the length of the CAR T-cell stay (Figure 2): history of transplant, treatment with tisa-cel, and** treatment in a **university center**

**CLCC French cancer centers*
***PSPH Participant in the Public Hospital Service*

Figure 2. Predictors of the CAR T-cell stay duration



[a]Effects for center experience are presented in number of days (e.g., center with high experience have a length of stay 1.3 days shorter than the average).

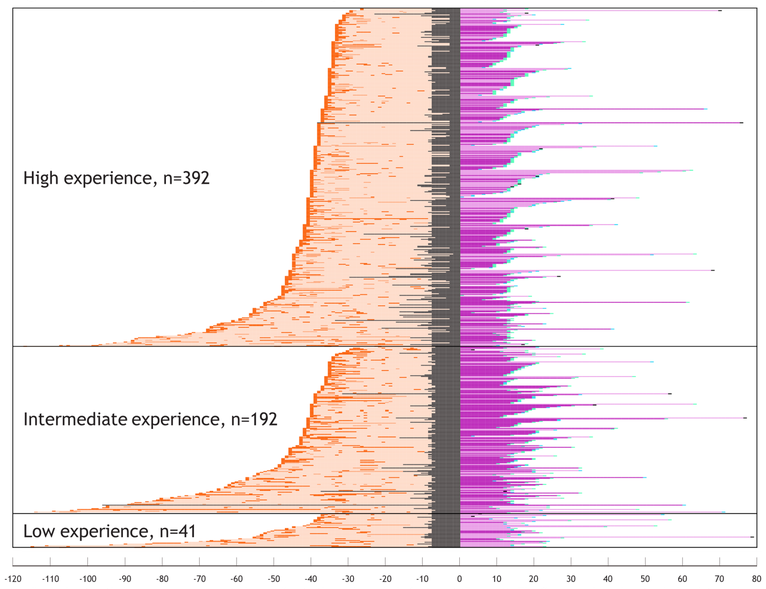
- **Post-infusion stay management.**

Among the 901 patients treated with axi-cel and tisa-cel, 674 returned home after hospitalization, 193 were transferred to another center, and 34 died. The following analysis concerns the 867 patients that were alive after the hospitalization.

- **The center's experience and the molecule had a statistically significant impact on post-infusion stay management.**
  - **Center's experience**. 64.1% of patients who were discharged at home were hospitalized in a center with high experience while only 53.4% when transferred.
  - **Molecule.** 42.1% of the patients who were discharged at home were treated with tisa-cel versus 28.5% when transferred.
- **After running the multivariate analysis, the molecule and the experience of the center remained the main determinants of the post-infusion stay management. Patients treated by tisa-cel were 75% more likely to be discharged at home (OR* = 0.57). Centers with higher experience showed a higher probability to be discharged at home than the average (+12,9%).**

**OR Odd Ratio*

Figure 3. Patient's journey by experience (in days from the index date)



** Individual patient's journey are represented according to the main period of interest (Figure 1). The figure is aligned on the index date and stratified by level of center's experience.*

Conclusion

- Patient characteristics data were consistent with data in the literature.[10-12]
- The mean duration of post-dose management of CAR T-cell was longer than the recommendations of the EHA (14 days) and SFGM-T*(10 days) with a duration of approximately 18 days.
- The experience of the CAR T-cell center had a strong influence on the patient's journey with:
  - A shorter duration of the bridging therapy
  - A higher probability of attending another center for the bridging therapy
  - A shorter length of CAR T-cell infusion stay
  - A higher probability of being discharged at home

  However, baseline characteristics are limited in the PMSI, few of them were used in the model.
- It would be interesting to observe if these trends are confirmed in 2022, as more qualified centers open to improve access to CAR T-cell treatment.

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- All authors contributed to and approved this poster.

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