



## **Prolonged thrombocytopenia after CAR T-cell therapy: the role of thrombopoietin receptor agonists**

Gaëlle Drillet, Faustine Lhomme, Sophie de Guibert, Guillaume Manson,  
Roch Houot

### **► To cite this version:**

Gaëlle Drillet, Faustine Lhomme, Sophie de Guibert, Guillaume Manson, Roch Houot. Prolonged thrombocytopenia after CAR T-cell therapy: the role of thrombopoietin receptor agonists. *Blood Advances*, 2023, 7 (4), pp.537-540. 10.1182/bloodadvances.2022008066 . hal-03901600

**HAL Id: hal-03901600**

**<https://univ-rennes.hal.science/hal-03901600>**

Submitted on 15 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Prolonged thrombocytopenia after CAR T-cell therapy:**  
2 **the role of thrombopoietin receptor agonists**

3  
4 Gaëlle Drillet<sup>1</sup>, Faustine Lhomme<sup>1</sup>, Sophie De Guibert<sup>1</sup>, Guillaume Manson<sup>1\*</sup>, Roch Houot<sup>1, 2\*</sup>

5  
6 <sup>1</sup> Department of Hematology, CHU de Rennes, Université de Rennes, Rennes, France

7 <sup>2</sup> INSERM U1236, Rennes, France

8  
9 *\*Equal contribution*

10  
11 **Corresponding author:**

12 Prof. Roch Houot

13 Department of Hematology

14 CHU Rennes

15 2 rue Henri Le Guilloux

16 35033 Rennes Cedex 9

17 France

18 Tel: +33 (0)2 99 28 42 26

19 Fax: +33 (0)2 99 28 41 61

20 E-mail: [roch.houot@chu-rennes.fr](mailto:roch.houot@chu-rennes.fr)

21  
22 Contact the corresponding author for data sharing: [roch.houot@chu-rennes.fr](mailto:roch.houot@chu-rennes.fr).

23  
24 **Manuscript word count: 1048**

25 **Tables and figures: 2**

26 **Supplemental Figures & Tables: 1**

27 **References: 21**

Chimeric Antigen Receptor T-cells (CAR T-cells) are associated with early (such as cytokine-release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]) and late toxicities. Delayed side effects include prolonged cytopenia and hypogammaglobulinemia. Although hypogammaglobulinemia has been well anticipated due to the expected on-target toxicity of the CD19-directed CAR T-cells, prolonged cytopenias have been initially underestimated (1,2). Their pathophysiology remains poorly understood and their optimal management is yet unknown. Prolonged and profound thrombocytopenia occurring after CAR T-cells infusion have been frequently reported in clinical trials and real-world studies (Supplementary Tables S1 and S2). In ZUMA-1, 24% of patients treated with axicabtagene-ciloleucel (Axi-cel) for a Diffuse Large B-cell Lymphoma (DLBCL) experienced grade 3 or 4 thrombocytopenia at day 30 after CAR T-cells infusion, and 7% at day 90 (3). In the real-world experience, Logue *et al* reported the outcome of 70 patients with B-cell lymphoma receiving Axi-cel in a single center, retrospective study. Grade 3 or 4 thrombocytopenia was found in 26% of patients at day 30, and 5% at day 90 (4). In a multicentric, retrospective study of DLBCL patients treated with axi-cel, Rejesky *et al*. described the biphasic temporal course of CAR T-cells associated cytopenias. Following hematologic recovery post-chemotherapy, neutrophils and platelets counts decreased after 3 weeks, reaching a nadir around 6 weeks after CAR T-cells infusion (2). Thrombopoietin receptor agonists (TPO-RA) have been approved for the treatment of immune thrombocytopenic purpura (ITP) and severe aplastic anemia (AA). They have also been used for the treatment of thrombocytopenia following chemotherapy or allogeneic stem cell transplantation (5). However, the role of TPO-RA in the management of prolonged thrombocytopenia after CAR T-cell therapy remains unknown.

Here, we retrospectively analyzed the outcome of lymphoma patients treated with CD19 CAR T-cells who developed prolonged and/or profound thrombocytopenia and who received TPO-RA at our center (University Hospital of Rennes). Patients were included if they had received at least one platelet transfusion after CAR T-cell infusion for a platelet count below  $20 \times 10^9/L$  and were treated with TPO-RA. Patients who relapsed after CAR T-cells were censored at the time of salvage therapy. Platelet recovery was defined as two consecutive platelet counts above  $50 \times 10^9/L$ . The study was approved by the Ethics Committee of the University Hospital of Rennes (study MR-004) and performed according to the Declaration of Helsinki.

Between September 2019 and October 2021, 71 patients were treated with Axi-cel, tisagenlecleucel (Tisa-cel) or brexucabtagene-autoleucel (Brexaca-cel) for DLBCL or Mantle Cell Lymphoma (MCL) and followed at our center. Grade 3 or 4 thrombocytopenia occurred in 46% of patients at 1 month, 25% at 2 months and 15% at 3 months after CAR T-cell infusion. The median CAR-HEMATOTOX score was

2. Overall, 62% of the patients presenting with a grade 3 or 4 thrombocytopenia after one month had a high CAR-HEMATOTOX score ( $\geq 2$ ). Among all 71 patients, 11 (15.5%) were treated with TPO-RA (patients' characteristics are presented in Table 1). All patients had been treated with Axi-cel for a DLBCL except two patients who were treated with Brexu-cel for a MCL (patient 5 and 8). No patient had been transplanted before CAR T-cell therapy. The median CAR-HEMATOTOX score was 3. Ten patients were treated with eltrombopag at 75mg per day and one patient received Romiplostim at 10ug/kg per week (patient 8). TPO-RA were started at a median of 27 days after CAR T-cells infusion and the median duration of treatment with TPO-RA was 97 days. Four patients were treated with an anticoagulant therapy (patient 2, 4, 10, and 11). As a result, they had a higher transfusion threshold (platelets below  $50.10^9/L$ ) and a higher platelet transfusion rate. Platelet transfusion independency was achieved after a median of 17 days following TPO-RA initiation and 46 days from CAR T-cell infusion. Platelet recovery was achieved after a median of 46 and 76 days following TPO-RA initiation and CAR T-cell infusion, respectively. At the time of analysis, only one patient (patient 2) has not achieved transfusion independency, 6 months after CAR T-cell infusion (Figure 1). In our cohort, bone marrow aspirate was performed in 5 patients : it showed a hypoplastic bone marrow with rare megakaryocytes in three patients and a normal bone marrow and megakaryocytes density in two patients. One patient relapsed at 3 months after CAR T-cells (patient 10) and was censored at the initiation of the oral chemotherapy. All the others were on remission after a median follow-up of 274 days. We did not observe any clinically significant adverse event which might have been related to TPO-RA, notably no thromboembolic event.

TPO-RA demonstrated efficacy in ITP and AA. Here, we evaluated the efficacy of TPO-RA in patients treated CAR T-cells. In our cohort, patients treated with TPO-RA achieved a platelet recovery after a median time of 46 days and transfusion independency was achieved after a median of 17 days following initiation of TPO-RA. In chronic ITP patients treated with TPO-RA (eltrombopag at 50-75mg per day), the median platelet count increased above  $53.10^9/L$  at day 15 (6,7). In severe AA (8), patients received eltrombopag at a higher dose of 150mg per day, along with immunosuppressive therapy. Platelet transfusion independency was achieved after a mean time of 40 days following randomization and 26 days following TPO-RA initiation ( TPO-RA was started 14 days after randomization). Prolonged cytopenias following CAR T-cells therapy usually recover spontaneously after a few weeks or months. Thus, it is difficult to formally demonstrate that TPO-RA contributed to reduce the duration of platelets recovery and/or transfusion needs in a retrospective study. However, the rapid improvement of thrombocytopenia in most patients, despite a high CAR-HEMATOTOX score, suggests some benefit of TPO-RA. Interestingly, TPO-RA were found to improve trilineage hematopoiesis in refractory patients with aplastic anemia, despite high levels of

endogenous thrombopoietin (9). Furthermore, a recent study showed that TPO-RA suppressed the inhibitory signal mediated by IFN- $\gamma$  in hematopoietic stem cells *in vitro* (10). The impact of TPO-RA on the three hematopoietic lineages through an anti-inflammatory effect may be of importance to treat prolonged cytopenias associated with CAR T-cell therapy.

Overall, our study is the first to report the effect of TPO-RA on prolonged CAR T-cell associated cytopenias. Our results suggest a possible benefit of TPO-RA in these patients to reduce the duration of platelet recovery and transfusion needs. However, prospective, randomized studies are warranted to formally evaluate the benefit of TPO-RA in this situation.

#### Author contribution statement

All authors have reviewed and approved the final manuscript.

#### Conflict-of-interest:

GD received honoraria from Janssen.

FL received honoraria from Gilead Sciences, Kite, Roch, and Janssen.

SDG received honoraria from Gilead Sciences, AbbVie, and Janssen.

GM received honoraria from Bristol-Myers Squibb.

RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene.

#### References

1. Fried S, Avigdor A, Bielorai B, Meir A, Besser MJ, Schachter J, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant.* oct 2019;54(10):1643-50.
2. Rejeski K, Perez A, Sesques P, Hoster E, Berger C, Jentzsch L, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood.* 16 déc 2021;138(24):2499-513.
3. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *The Lancet Oncology.* janv 2019;20(1):31-42.
4. Logue JM, Zucchetti E, Bachmeier CA, Krivenko GS, Larson V, Ninh D, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica.* 2021;106(4):978-86.
5. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. *Haematologica.* 1 juin 2019;104(6):1112-23.

- 1 6. Bussel JB, Provan D, Shamsi T, Cheng G, Psaila B, Kovaleva L, et al. Effect of  
2 eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic  
3 thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *The*  
4 *Lancet*. 21 févr 2009;373(9664):641-8.
- 5 7. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for  
6 management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised,  
7 phase 3 study. *The Lancet*. 29 janv 2011;377(9763):393-402.
- 8 8. Peffault de Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M, et al.  
9 Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia. *N Engl J Med*. 6  
10 janv 2022;386(1):11-23.
- 11 9. Zhao X, Feng X, Wu Z, Winkler T, Desmond R, Olnes M, et al. Persistent elevation of  
12 plasma thrombopoietin levels after treatment in severe aplastic anemia. *Exp Hematol*.  
13 févr 2018;58:39-43.
- 14 10. Alvarado LJ, Huntsman HD, Cheng H, Townsley DM, Winkler T, Feng X, et al.  
15 Eltrombopag maintains human hematopoietic stem and progenitor cells under  
16 inflammatory conditions mediated by IFN- $\gamma$ . *Blood*. 9 mai 2019;133(19):2043-55.
- 17 11. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al.  
18 Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia.  
19 *N Engl J Med*. 1 févr 2018;378(5):439-48.
- 20 12. Shah NN, Lee DW, Yates B, Yuan CM, Shalabi H, Martin S, et al. Long-Term Follow-  
21 Up of CD19-CAR T-Cell Therapy in Children and Young Adults With B-ALL. *J Clin*  
22 *Oncol*. 20 mai 2021;39(15):1650-9.
- 23 13. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al.  
24 Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma.  
25 *New England Journal of Medicine* [Internet]. 1 déc 2018 [cité 24 oct 2021]; Disponible  
26 sur: <https://www-nejm-org.passerelle.univ-rennes1.fr/doi/10.1056/NEJMoa1804980>
- 27 14. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al.  
28 Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell  
29 lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *The*  
30 *Lancet*. 19 sept 2020;396(10254):839-52.
- 31 15. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-  
32 Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *New England Journal*  
33 *of Medicine*. 2 avr 2020;382(14):1331-42.
- 34 16. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al.  
35 Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2  
36 ELARA trial. *Nat Med*. 17 déc 2021;1-8.
- 37 17. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al.  
38 Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma  
39 (ZUMA-5): a single-arm, multicentre, phase 2 trial. *The Lancet Oncology*. 1 janv  
40 2022;23(1):91-103.

18. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *The Lancet*. 24 juill 2021;398(10297):314-24.
19. Pasquini MC, Hu ZH, Curran K, Laetsch T, Locke F, Rouce R, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv*. 4 nov 2020;4(21):5414-24.
20. Dourthe ME, Rabian F, Yakouben K, Cabannes A, Chevillon F, Chaillou D, et al. Safety and Efficacy of Tisagenlecleucel (CTL019) in B-Cell Acute Lymphoblastic Leukemia in Children, Adolescents and Young Adults: The French Experience. *Blood*. 13 nov 2019;134:3876.
21. Sesques P, Ferrant E, Safar V, Wallet F, Tordo J, Dhompas A, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. *American Journal of Hematology*. 2020;95(11):1324-33.

**Table 1.** Patients' characteristics

Number of patients		11
Median age, years (range)		64 (41 ; 75)
Disease	DLBCL	9/11
	MCL	2/11
CAR-T cell	Axi-cel	9/11
	Brexu-cel	2/11
Median CAR-HEMATOTOX score (range)		3 (0;5)
Type of TPO-RA	Eltrombopag	10/11
	Romiplostim	1/11
Median follow-up from CAR T-cells infusion, days (range)		274 (90;828)
Median platelets count at 1 month of TPO-RA initiation, x 10 <sup>9</sup> /L (range)		28 (13 ; 295)
Median platelets count at 2 months of TPO-RA initiation, x 10 <sup>9</sup> /L (range)		60 (8 ; 226)
Median platelets count at 3 months of TPO-RA initiation, x 10 <sup>9</sup> /L (range)		68 (17 ;162)

Median time between CAR-T infusion and start of TPO-RA, days (range)	27 (14 ; 45)
Median duration of TPO-RA, days (range)	97 (27 ; 180)
Number of patients free of platelets transfusion after TPO-RA	10/11*
Median duration between start of TPO-RA and last transfusion, days (range)**	17 (1 ; 65)
Median duration between start of TPO-RA and platelet recovery, days (range)**	46 (18 ; 100)
Median duration between CAR T-cells infusion and last transfusion, days (range)**	46 (21 ; 104)
Median duration between CAR T-cells infusion and platelet recovery, days (range)**	76 (53 ; 130)

CAR T-cells, Chimeric Antigen Receptor T-cells; TPO-RA, Thrombopoietin receptor agonist; DLBCL, Diffuse Large B-cell Lymphoma; MCL, Mantle Cell Lymphoma

\*Patient 2 since still transfused at 6 months after CAR T-cell infusion.

\*\* Patient 2 excluded since still transfused at 6 months after CAR T-cell infusion.

Platelet recovery was defined as two consecutive platelet counts above  $50.10^9/L$ .

#### Figure 1 legends

A. Median platelets counts before and after TPO-RA initiation for the entire cohort  
 Median platelet counts of the 11 patients are represented from day 42 before TPO-RA initiation (D-42) until day 90 after TPO-RA initiation (D90). B. Individual platelet counts before and after TPO-RA initiation. Platelet counts of the 11 patients treated with TPO-RA are showed from day 42 before TPO-RA initiation (D-42) until day 90 after TPO-RA initiation (D90). CAR T-cell infusion is represented with a black dot. The platelet counts before CAR T-cell infusion are represented with dashed lines and those after infusion are represented with continuous lines. C. Platelet transfusion rates before and after TPO-RA initiation. The black bullet point represents CAR T-cells infusion. Each red bar represents a platelet transfusion.



