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Single Center Experience on Management of CAR-T Related Thrombocytopenia

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Abstract

Chimeric Antigen Receptor (CAR) T cells therapy is the standard of care for refractory/recurring Non-Hodgkin B Cell Lymphoma (R/R NHL). Nowadays increasing experience on CAR-T therapy shows that early-onset toxicity (cytokine releasing syndrome and neurotoxicity) is manageable, shifting the attention to late-onset toxicities like cytopenia and infections. Grade ≥ 3 thrombocytopenia occurs in almost one third of patients and still represents an unmet clinical need. Thrombopoietin mimetic (TPOm) Romiplostim, thanks to the results in Aplastic Anemia (AA) and immune thrombocytopenia, is off-label-used in this setting. Our experience on 7 patients with grade ≥ 3 thrombocytopenia, over a cohort of 21 patients who undergone CAR-T therapy between January 2021 and December 2022, confirms that management with Romiplostim is efficient and feasible.

Introduction

CAR-T cell therapy represents the new resource for treatment of refractory/recurring Non-Hodgkin B Cell Lymphoma (R/R NHL).

As demonstrated by data of SCHOLAR-1 study, R/R NHL have a very poor survival and CAR-T cell therapy offers chance to achieve, in 40% of the cases, Overall Survival (OS) of 2 years [1-3].

CAR-T cell therapy uses patient- *ex vivo*-derived T-cells that, thanks to a bio-engineering process, are able to recognize and amplify an immune reaction against patient-own-disease.

The extracellular domain of chimeric receptor, through the antigen-specific single chain variable Fragment (scFv), is able to recognize the CD19 antigen, meanwhile the costimulatory domain, with molecules like CD28 and 41BB, is able to boosts the immune attack [4].

Adaptive immunotherapy is, otherwise, hampered by a unique toxicity profile.

Initially, early onset toxicity like the Cytokine Release Syndrome (CRS) and the Immune Cell Effector Neurotoxicity Syndrome (ICANS), have almost monopolize practitioner's attention.

Thanks to increasing experience, late adverse effects are emerging as substantial clinical obstacles.

Cytopenia was a common adverse effect in pivotal trials of available CAR-T cell therapies, with any grade cytopenia occurring in 44%, 84% and 60% of patients treated with Tisa-cel, Axi-cel and Brexu-cel respectively [2,5,6].

CAR-T-related cytopenia has a typical biphasic pattern with brief-term cytopenia, dues to lymphodepleting treatment, and long-term cytopenia, dues to direct cellular immunotherapy effect and following cytokines-related perturbations of inflammation network.

"Real word" retrospective studies confirm that long-term hematological toxicity is a remarkable physician's concern.

Recent systematic review and meta-analysis through studies including 2004 patients demonstrated an incidence of any grade neutropenia, thrombocytopenia and anemia of 80%, 61% and 68% respectively, higher incidence in younger patients, ones with ≥ 4 median previous lines and patients treated with CD28-costimulatory-domain product [7].

Incidence of grade ≥ 3 cytopenia was 60% for neutropenia, 33% for thrombocytopenia and 32% for anemia.

Neutropenia's management has already focused the attention of practitioners, leading the use of

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G-CSFs as therapy and/or prophylaxis [8].

Anemia and thrombocytopenia are managed through transfusions of irradiated components and using growth factors as EPO-similar and TPO-mimetics (TPOm).

Unfortunately, management of thrombocytopenia is often challenging due to the paucity of platelet components.

Herein our experience with CAR-T related thrombocytopenia and how we managed it.

Methods

We undertook a retrospective analysis of all patients who received Tisa-cel, Axi-cel and Brexu-cel for treatment of R/R PMBL, DLBCL, transformed Follicular Lymphoma (tFL) and Mantle Cell Lymphoma (MCL) between January 2021 and December 2022.

Whole patients' characteristics are listed in Table 1 and Table 2, while in Table 3 are showed the main features per diagnosis and CAR-T product.

All procedures followed are in accordance with the standard of local ethics and with Helsinki declaration of 1975 (in its most recently amended version). Informed consent was obtained from all patient.

Data collection was daily-made during the inpatients staying (regularly until the 15th days post-CAR T infusion), otherwise, in absence of complications, weekly the first month, every two weeks the subsequent two months and monthly until the sixth month. Then every three months whole first year and twice a year successively.

Twenty-one patients received CAR-T cell therapy and median follow up of 238 days (range 22-704 days); nine patients received Axi-cel, seven patients received Tisa-cel and five patients received Brexu-cel. 66% were males.

Fifty-seven percent had DLBCL or tFL, 19% had PMBCL and 24% had MCL. Twenty-nine percent were treated on second relapse and seventy-one percent on third or more relapse (range 3-7 previous lines). Median previous lines for DLBCL, PMBL and MCL cohorts were 3.5, 2 and 4 respectively, 3 for Tisa-cel and Axi-cel cohorts both.

Sixty-six percent undergone High Dose Therapy and Autologous Stem Cell Transplant (HDT-ASCT).

Median age was 62 years (range 22-76) with an older median age in Tisa-cel (64 years) and Brexu-cel (62 years) cohorts than in Axi-cel ones (43 years).

Median age in DLBCL and PMBL cohort was 64 and 26.5 years respectively.

CAR-T were administered two days after the end of proper Lymphodepleting therapy (LD) lasting three days [9,10].

Median number of CAR-T cells infused was 1.82×10^8 in whole study population; 2.2×10^8, 1.27×10^8, 1.28×10^8, 2.7×10^8 and 1.4×10^8 for DLBCL, PMBL, Brexu-cel, Tisa-cel and Axi-cel subgroups respectively, although Brexu and Axi-cel company (Gilead®) provides just an estimate of CAR-T cells with a standard value of 2×10^6 cells/kg.

CRS and ICANS were evaluated according to American Society for Transplantation and Cellular Therapy (ASTCT) scale [11].

CRS of any grade occurred in 90% of patients, 28% of grade 3. No grade 4 CRS was observed. ICANS occurred in 2 patients (9%), respectively of grade 3 and grade 1, both resolved with appropriate steroid treatment and Brexu-cel-related.

We evaluated Platelet Counts (PC) from day 1 of LD chemotherapy to last known follow-up.

Median PC at the start of LD was 159.000/mmc (range 66.000-602.000/mmc).

Thrombocytopenia was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) grading.

Three patients were already thrombocytopenic before LD therapy, respectively two patients (9%) and 1 patient (5%) with grade 1 and 2 thrombocytopenia.

We focused on hematotoxicity of grade 3, or rather PC<50.000/mmc, and grade 4, or rather PC<25.000/mmc.

Grade ≥ 3 thrombocytopenia occurred in 33% of patients, specifically three patients had grade 3 and five patients grade 4. Three patients were treated with tisa-cel, three patients with axi-cel (2 of the latter because of PMBL histology) and two patients with brexu-cel.

Grade 3 and 4 thrombocytopenia showed a median onset of 14 days (range 2-60) and 21 days (20-31) from CAR-T infusion, respectively.

CMV-serotype matched platelets' apheresis units were administered, when available, in case of PC<20.000/mmc, regardless of hemorrhagic symptoms.

Romiplostim (Nplate®) was given to more than 1-week lasting grade ≥ 3 thrombocytopenic patients.

TPOm-treatment ended after second detection of PC>50.000/mmc on weekly sampling. No tapering was planned.

One case of thrombocytopenia lasted less than one week, so, seven patients were treated with weekly TPO-mimetic Romiplostim at the initial dose of 1 mcg/kg and progressive dosage increase by 1 mcg/kg/weekly in case of lacking of response.

Results

TPOm-treated cohort had a median of 5 previous lines of treatment and median age of 62 years.

TPOm-not-treated cohort (Control cohort) shows a median of 3 previous lines and same median age.

A median of 6 doses of romiplostim were administered (range 3-17) with median posology of 4 mcg/kg (range 1-8 mcg/kg).

Tisa-cel's subgroup reveals a median of 13 administrations, 4.5 administrations in Axi-cel and 4 administrations in Brexu-cel ones.

DLBCL's subgroup were treated with a median of 9.5 administrations while PMBL's 3 administrations.

Median posology of romiplostim was 8 mcg/kg in Tisa-cel's subgroup, 3.5 mcg/kg in Axi-cel and Brexu-cel ones both, 6 mcg/kg in DLBCL's and 3 mcg/kg in PMBL's subgroups.

Median PC, at the beginning of romiplostim's therapy was 26.000/mmc in the entire cohort while; 16.000/mmc in Tisa-cel's group, 27.500/mmc in Axi-cel's group, 26.500/mmc in Brexu-cel's ones. DLBCL's patients exhibited a median PC at the start of treatment of

Table 1: Cohort's characteristics.

Characteristic	N=21
Median age (range)	62 (22-76)
Sex M (%)	14 (66%)
Sex F (%)	7 (33%)
DLBCL	12 (57%)
PMBCL	4 (19%)
MCL	5 (24%)
2° relapse	6 (29%)
≥ 3° relapse	11 (71%)
HDT-AutoSCT N (%)	14 (66%)
Axi-cel N (%)	9 (43%)
Tisa-cel N (%)	7 (33%)
Brexu-cel N (%)	5 (24%)

DLBCL: Diffuse Large B Cell Lymphoma; PMBCL: Primary Mediastinal B Cell Lymphoma; MCL: Mantle Cell Lymphoma; HDT-AutoSCT: High Dose Chemotherapy and Autologous Stem Cell Transplant

17.000/mmc, 37.000/mmc for PMBL's ones.

All mentioned data are showed in Table 4, 5.

PC nadir was reached after the beginning of TPOm treatment in 71% of patients, showing median latency of 4 days; same latency occurred in DLBCL's and PMBL's both, 3 and 3.5 days in Axi-cel's and Brexu-cel's respectively, while it was almost the double in Tisa-cel's subgroup (7 days).

Median PC nadir was 14.000/mmc in entire cohort; Tisa-cel, Axi-cel and Brexu-cel 21.500/mmc, 12.500/mmc and 19.000/mmc respectively.

Control cohort reached a PC nadir 17.5 days after CAR-T infusion with a median PC of 97.500/mmc.

Six of seven patients ended successfully the treatment, achieving steadily PC>50.000/mmc.

Median TPOm treatment duration is 84 days (range 29-252 days) and median PC at the end of the study period is 70.000/mmc (range 34.000-132.000/mmc). Median posology is 4 mcg/kg (range 8-4), almost the same in the subgroups except that Tisa-cel' ones with 8 mcg/kg, DLBCL's with 6 mcg/kg and PMBL's with 3 mcg/kg.

That one who didn't respond to treatment died because of progression of disease and his follow up ends on 154th day post CAR-T infusion, after 13 administrations of Romiplostim and a PC of 39.000/mmc at his last follow up.

No one showed side effects related to TPOm-treatment during the study period nor thrombosis.

Because of a CMV-negative serotype, the first patient had an additional obstacle in matching of blood components.

Only 2 patients received transfusion support during the study-period: one patient received 1 unit while the other one 6 units. The first patient received Axi-cel while the second one Tisa-cel. No major bleeding occurred.

One patient experienced relapse of thrombocytopenia 282 days after the last TPOm administration without evidence of relapse/

Table 2: Patients' characteristics.

ID	Dx	Age	Previous lines	Follow up (days)	Axi/Tisa	PC pre-LD (/mmc)	PC nadir (/mmc)	Day PC nadir	TPOm Yes/no	AP transfusions
1	DLBCL	54	3	604	Axi	141.000	50.000	5	No	/
2	DLBCL	64	4	298	Tisa	127.000	62.000	74	No	/
3	DLBCL	64	4	438	Axi	226.000	68.000	32	No	/
4	DLBCL	65	5	288	Tisa	75.000	40.000	67	Yes	/
5	PMBCL	26	2	260	Axi	123.000	28.000	4	No	/
6	PMBCL	43	7	321	Axi	151.000	11.000	20	Yes	1
7	PMBCL	22	2	310	Axi	134.000	86.000	4	No	/
8	DLBCL	28	5	365	Tisa	169.000	3.000	24	Yes	6
9	DLBCL	64	3	154	Tisa	191.000	15.000	31	Yes	/
10	PMBCL	27	2	261	Axi	217.000	196.000	47	No	/
11	DLBCL	38	2	179	Axi	177.000	133.000	28	No	/
12	DLBCL	26	3	168	Tisa	113.000	142.000	64	No	/
13	DLBCL	69	2	156	Tisa	159.000	109.000	2	No	/
14	DLBCL	68	4	98	Axi	353000	312000	2	No	/
15	DLBCL	69	4	79	Axi	66000	14000	23	Yes	/
16	DLBCL	66	3	24	Tisa	98000	68000	24	No	/
17	MCL	62	6	104	Brexu	118000	11000	27	Yes	/
18	MCL	60	5	106	Brexu	229000	167000	11	No	/
19	MCL	59	2	71	Brexu	80000	27000	29	Yes	/
20	MCL	76	3	37	Brexu	602000	215000	7	No	/
21	MCL	68	4	22	Brexu	313000	52000	25	No	

Patient's values per: Identification code (ID), Histological diagnosis (Dx), age, number of previous therapy lines, days of follow up, Axi or Tisa-cel treatment, Platelet Count (PC) before Lymphodepleting Therapy (LD), lowest Platelet Count reached through study period (PC nadir) and day from CAR-T infusion (Day PC nadir), Thrombopoietin mimetics-treated or not (TPOm Y/N), units of Apheresis Platelets transfused (AP)

Table 3: Median age and median previous lines per subgroups.

	DLBCL (12)	PMBL (4)	MCL (5)	Tisa-cel (9)	Axi-cel (7)
Median age (range)	64 (26-69)	26.5 (22-43)	62 (59-76)	64 (26-69)	43 (22-69)
Median previous lines (range)	3.5 (2-5)	2 (2-7)	4 (2-6)	3 (2-5)	3 (2-7)

DLBCL: Diffuse Large B Cell Lymphoma; PMBCL: Primary Mediastinal B Cell Lymphoma, MCL: Mantle Cell Lymphoma

Table 4: TPOm treated cohorts and subgroups' characteristics.

	N pts (%)	N admin (range)	TPOm dose mcg/kg (range)	pre-TPOm PC/ mmc (range)	TPOm lasting Days (range)	Onset day G ≥ 3 TTP (range)	end-treatment PC/mmc (range)
Entire cohort (21)	7 (33%)	6 (1-17)	4 (1-8)	26.000 (15.000-46.000)	84 (29-252)	15 (6-60)	70.000 (34.000-132.000)
DLBCL (12)	4 (25%)	9.5 (4-17)	6 (3-8)	17.000 (15.000-46.000)	109.5 (84-252)	14 (12-60)	80.000 (34.000-132.000)
PMBL (4)	1 (25%)	3	3	37.000	29	9.5 (2-17)	52.000
MCL (5)	2 (40%)	4 (1-7)	3.5 (1-6)	26.500 (26.000-27.000)	57 (29-85)	17.5 (6-29)	79.000 (50.000-108.000)
Tisa-cel (7)	3 (43%)	13 (4-17)	8 (3-8)	16.000 (15.000-46.000)	135 (84-252)	13 (12-60)	90.000 (34.000-132.000)
Axi-cel (9)	2 (22%)	4.5 (3-6)	3.5 (3-4)	27.500 (18.000-37.000)	50.5 (29-72)	15 (2-17)	61.000 (52.000-70.000)

Values per: Absolute number of patients TPOm-treated, median of number of TPOm-administrations, median of TPOm-dosing, median's Platelet Count (PC) before starting TPOm-treatment, TPOm-duration's treatment, Onset Day of Grade ≥ 3 Thrombocytopenia (TTP) after CAR-T, Platelet Count (PC) at the end of TPOm-treatment; DLBCL: Diffuse Large B Cell Lymphoma; PMBCL: Primary Mediastinal B Cell Lymphoma; MCL: Mantle Cell Lymphoma

Table 5: TPOm treated cohort.

Follow-up days (range)	Median lines (range)	Median age (range)	TPOm treated N patients	Target reached N patients (%)
154 (71-321)	5 (2-7)	62 (28-69)	7	6 (86%)

Characteristic of patients treated with TPOm per: Days of follow up, median previous lines of therapy, median age, number of patients who reached the target (PLT>50.000/mmc in two subsequent detections)

progression of lymphoma. Due to logistic reasons, TPOm treatment with Eltrombopag started immediately at his origin spoke center. Treatment is still ongoing.

Discussion and Conclusion

The underlying patho-mechanism of post-CAR-T cytopenia is a matter of debate and, thanks to spreading use of cellular therapies and increased experience by practitioners, in depth-analysis on its management is a growing requirement.

Our experience on twenty-one patients reports an incidence of ≥ grade 3 thrombocytopenia of 33% that is in line with literature's data; one of seven patients recovered spontaneously.

We chose Romiplostim because of its high response in Immune Thrombocytopenic Purpura (ITP) and Aplastic Anemia (AA) and for its subcutaneous way of administration that reduces risk of missed doses due to LD-related nausea and/or vomit, ensuring correct absorption and distribution of the drug [12,13].

The vast majority (86%) of patients who undergone TPOm-treatment reached the target of PC>50.000/mmc, lasting a median of 84 days and median dose of 4 mcg/kg. Median PC at first and last day of administration is 26.000/mmc and 70.000/mmc, respectively.

Romiplostim doesn't show an immediate action, as pointed by latency of 4 days between drug's first administration and PC nadir in 70% of cases.

Although the paucity of our data, posology and latency of action is almost doubled in Tisa-cel-treated patients than others subgroups.

Median age of TPOm-treated cohort is 62 years, same as in Control cohort, DLBCL's, Tisa-cel's and Brexu-cel's subgroups, while it's lower in PMBL's and Axi-cel ones with 26.5 and 43 years respectively.

Although the paucity of our data, different response to TPO-treatment could not be influenced by age while disease's histology and 4-1BB-costimulatory domain-products could play a role.

Furthermore, cellularity of CAR-T products, together with their different co-stimulatory domains, could influence the medullary microenvironment and platelets' toxicity.

According to Luo's metanalysis, our casuistry shows more previous treatment's lines before CAR-T in severe thrombocytopenic cohort than in the control ones.

Late-onset effect, along with high overall response, offers the possibility to move up the TPOm-support's timing on PC between 50.000-100.000/mmc yet.

An early use of TPOm could increase the availability of drug receptor thanks to, probably, a higher amount of megakaryopoiesis precursors in the mild-thrombocytopenic phase than in the severe-ones. This timing could be suitable especially on high-risk patients according to emergent score as CAR-HEMATOTOX [14].

Only two patients needed transfusion support and one of them needed a considerable amount of irradiated apheresis' units.

Recently, both in the setting of DLBCL and multiple myeloma, case reports experienced re-infusion of cryopreserved Autologous Stem Cells (ASC), left from a previous collection, on management of CAR-T pancytopenia [15,16].

This approach showed interesting results, achieving resolution of grade 4 pancytopenia in less than 15 days after ASC infusion; surely more data needing but not every patient can rely on this resource.

Therapy related cytopenia will occur more often in the future thanks to the emergence of cellular therapy and further studies, as randomized trials, can clarify the role of TPOm on CAR-T-related thrombocytopenia.

Moreover, thrombocytopenia can relapse over time, as showed on our casuistry.

Taken together, our clinical records show that thrombocytopenia management with Romiplostim could be feasible, efficient and, probably, improvable.

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