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Case Report

Single Center Experiences on Chimeric Antigen Receptor T-cell Therapy

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SUMMARY

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy) has emerged as a groundbreaking treatment for relapsed or refractory B-cell lymphomas and leukemia. This personalized immunotherapy has demonstrated high efficacy, with complete remission (CR) rates ranging from 40% to over 80% in aggressive forms of lymphoma. We presents three cases from MacKay Memorial Hospital, illustrating the benefits and challenges associated with CAR T-cell therapy. In the first case, a 53-year-old female with B-acute lymphoblastic leukemia achieved CR after CAR T-cell therapy, with CAR T-cells detectable for at least six months. The second case involved a 49-year-old female with diffuse large B-cell lymphoma who experienced severe cytokine release syndrome (CRS) and ultimately passed away due to complications. The third case featured a 62-year-old male with mantle cell lymphoma, who initially responded to CAR T-cell therapy but later relapsed and succumbed to disease complications. The article emphasizes the importance of effective management of side effects such as CRS and neurotoxicity, which can significantly impact patient outcomes. Individualized management strategies are crucial. Future directions for CAR T-cell therapy include exploring next-generation constructs, alternative targets beyond CD19, and combining other treatment modalities. In conclusion, while CAR T-cell therapy represents a significant advancement, ongoing research is essential to optimize patient selection and management strategies.

1. Introduction

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy) has emerged as a transformative treatment for lymphoma, particularly for patients with relapsed or refractory B-cell malignancies. This innovative approach harnesses the power of the patient's own immune system to target and eliminate cancer cells, offering several significant benefits.

CAR T-cell therapy is a form of personalized immunotherapy, where T-cells are genetically modified to express receptors that specifically target cancer cells. This tailored approach not only enhances the immune response against the tumor but also minimizes damage to healthy tissues, which is a common issue with conventional chemotherapy.

One of the primary advantages of CAR T-cell therapy is its high efficacy in achieving complete remission (CR) in patients who have not responded to traditional treatments. Clinical trials have demonstrated CR rates ranging from 40% to over 80% for patients with aggressive forms of B-cell lymphoma, such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma.[1,2] Moreover, some patients achieve long-term disease control, with reports indicating that certain individuals remain in remission for years following a single infusion of CAR T-cells.[3] This potential for durable remissions represents a paradigm shift in managing previously untreatable or hard-to-treat lymphomas.

While CAR T-cell therapy seems promising, we cannot neglect significant side effects such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and long-term hypogammaglobulinemia. Fortunately we now have effective management for these complications.

Here we present 3 cases of relapsed/refractory lymphomas undergoing CAR T-cell therapy in MacKay Memorial Hospital (MMH).

2. Case report

2.1. Case 1

This was a 53-year-old female who was diagnosed as B-acute lymphoblastic leukemia with Philadelphia chromosome in 2019. She received hyper-CVAD, prophylactic intrathecal therapy, and dasatinib (Bristol Myers Squibb, USA) 100 mg per day treatment first. 3 months later, due to persistent prolonged QTc despite decreased dasatinib dose, the dasatinib was replaced by imatinib 400 mg QD (TTY Biopharm, Taiwan), but 2 months later again replaced by ponatinib 45 mg QD (Takeda Pharmaceuticals, USA) from 2019/12 due to loss of major molecular response. Fortunately, the log BCR::ABL1 reached 10^{-5} from 2020/3 after using ponatinib for 3 months. Maintenance therapy with ponatinib, monthly vincristine and prednisolone were given. She did hot have a transplant due to lack of a proper donor.

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However, 15 months later in 2021/6, she relapsed with log BCR::ABL1 -1.4 and central nervous system (CNS) involvement. Once course of hyper-CVAD and intrathecal therapies were given but log BCR::ABL1 rose to -0.2. Total 1.8 mg/m^2 of inotuzumab ozogamicin (Pfizer, USA) was given on 2021/7/29, and she got 2nd complete remission with log BCR:: ABL1 -4.6 in 2021/9. To prevent further relapse, we decided to use compassionate CD19 CAR T-cell therapy from PELL BMT Ltd. Co., Taiwan. We harvested her lymphocytes on 2021/10/7. We performed lymphodepletion therapy on 2021/11/05 with fludarabine 25 mg/m^2/day, cyclophosphamide 300 mg/m^2/day for 3 days 12 weeks apart from inotuzumab, and infused CAR T-cells 1.5*10^6/kg on 2021/11/10 as day 0. After CAR T-cell infusion we monitored her signs of CRS and ICANS every 8 hours with a grading system suggested by American Society for Transplantation and Cellular Therapy (ASTCT). She had grade 2 CRS with fever >38 °C and hypoxia requiring low-flow oxygen 2 liters/min on day 3. We used empirical meropenem, teicoplanin, micafungin and gave her one dose of tocilizumab 8 mg/kg (350 mg) (Roche, Swiss) on day 5. The CRS gradually decreased from day 7.

Log BCR::ABL1 reached -5 one month later. The CAR T-cells was detectable in her blood for at least 6 months (Figure 1).

Till the last followed up on 2024/12/3, she remained in complete remission with log BCR::ABL1 -5.

2.2. Case 2

This was a 49-year-old female with diffuse large B cell lymphoma Lugano stage 4 involving left eye, the omentum, left kidney, and the urinary bladder in 2012/3. She received 8 cycles of R-CHOP and intrathecal therapies and reached 1st complete remission. 8 years later in 2020/5 she had relapsed lymphoma in brain, and received 7 cycles of rituximab plus high dose methotrexate (R-HDMTX). Stem cell harvest failed so we did not perform an autologous transplant. The 2nd complete remission lasted only for 4 months, and the lymphoma relapsed in the brain again in 2021/1. We gave her R-HDMTX plus high dose cytarabine (HDAC) for 5 cycles. She got 3rd complete remission.

However, 5 months later in 2021/11 the lymphoma relapsed in the brain again with symptoms of increased intracranial pressure. We decided to try compassionate CD19 CART therapy (PELL BMT Ltd. Co., Taiwan). After leukapheresis in 2022/1 we used whole brain radiotherapy for bridging, but the disease progressed with seizure so we participated tirabrutinib (Ono Pharmaceutical Co., Ltd., Japan) 480 mg QD from 2022/3/26, and she got 4th complete remission 1 month later. No more neurological symptoms during complete remission.

We infused CAR-T cells 4*10^6/kg on 2022/5/20 as day 0 after lymphodepletion therapy on 2022/5/15 with fludarabine 25 mg/m^2/day, cyclophosphamide 300 mg/m^2/day for 3 days. Before CAR T-cell infusion she had clear consciousness and did not have neurological symptoms. On day 2 fever started with mild hypotension and we gave 1st tocilizumab 525 mg and cefepime. The fever persisted and hypotension happened again on day 4 and we gave the 2nd tocilizumab 525 mg and replaced cefepime with meropenem. However, further hypotension, hypoxemic respiratory failure, and unarousable conscious disturbance started from day 5, compatible with grade 4 CRS and grade 4 ICANS. We gave 3rd tocilizumab 525 mg, dexamethasone 20 mg Q6H and ruxolitinib 5 mg BID, but the syndrome kept worsening, and finally she passed away on day 6. The chest computed tomography on day 5 to survey respiratory failure showed secretion in bilateral lower bronchi with consolidation in bilateral lungs. Fluid accumulatedin the oropharynx, and ascites, suggesting a capillary leak syndrome.

2.3. Case 3

This was a 62-year-old male with mantle cell lymphoma Lugano stage I at the left inguinal tumor. She received the bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone regimen (VR-CAP) from 2018/1 for 4 cycles, radiotherapy, and continued bortezomib treatment. The tumor only showed partial response and progressed 1.5 years later, and then we tried ibrutinib (AbbVie, USA) 560 mg QD from 2019/8. She reached 1st complete remission, but chose to rely on maintenant ibritunib rather than transplant.

She experienced 1st relapse half year later in 2020/12, with bone marrow involvement. 2nd complete remission was achieved after 3 cycles of rituximab, dexamethasone, cytarabine, cisplatin (R-DHAP) treatments. To get deeper lymphoma eradication she agreed transplant so we harvested stem cells after one course of rituximab, etoposide, methylprednisolone, cytarabine and cisplatin (R-ESHAP) and performed rituximab, carmustine, etoposide, cytarabine, melphalan (R-BEAM) followed by autologous stem cell transplant in 2021/6.

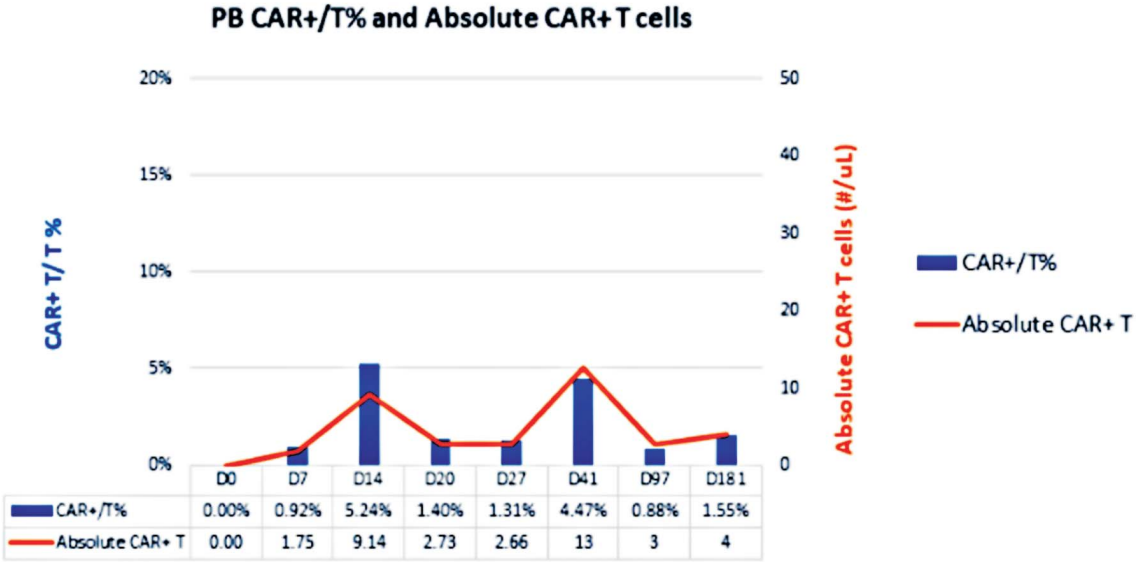

Figure 1. Dynamics of CAR T-cell in Case 1. CAR+ T/T%, the percentage of CAR T-cells among all T cells detected in the blood.

However, the 2nd relapse came half a year after the transplant in 2021/12, with a submandibular lymphadenopathy. Because of multiple relapses we decided to try compassionate CD19 CAR T-cell therapy (PELL BMT Ltd. Co., Taiwan). We harvested lymphocytes on 2022/03/21, meanwhile used imatinib to bridge to CAR T-cell infusion due to prior response. After lymphodepletion therapy on 2022/5/15 with fludarabine 25 mg/m^2/day, cyclophosphamide 300 mg/m^2/day for 3 days we infused CAR T-cells 1.49*10^6/kg on 2022/5/27. There was once fever on day 1 with hypotension rescued by fluid challenge indicating a grade 2 CRS, which was controlled by once tocilizumab 540 mg and empirical antibiotics. Followed CT 2 months later on 2022/7/1 showed partial response, and no bone marrow involvement. There were persistently detected CAR T-cells in blood even on day 84 (2022/8/19) (Figure 2).

However, 5 months later in 2022/10, lymphocytosis in blood happened, and bone marrow showed massive lymphoma relapse. We tried high-dose cytarabine, obinutuzumab, methotrexate, and glofitamab (2.5 mg, Roche, USA) from 2022/10–2023/3, but the disease was refractory. He died of sepsis due to neutropenia on 2024/4/18.

3. Discussion

We applied to the CD19 CAR T-cell therapy produced by PELL BMT Ltd. Co., Taiwan compassionate usage for these relapsed/refractory patients. One of the distinctive characteristics of PELL CD19 CAR T-cell therapy is that it contains multiple transmembrane domains,[20] which connect multiple intracellular costimulatory domains so it may induce more activating signals. Now it is under a multicenter, phase 1/2 clinical trial (ClinicalTrials.gov ID NCT05326243) starting from 2022.

The experiences documented in these cases from MacKay Memorial Hospital underscore the dual nature of CAR T-cell therapy as both a groundbreaking treatment modality and a complex clinical challenge. As we reflect on these cases, several key themes emerge regarding the efficacy, safety, and future directions of CAR T-cell therapy in leukemia and lymphoma treatment.

The complete remission observed in the cases, particularly in Case 1, illustrate the potential of CAR T-cell therapy to achieve durable responses in patients who have exhausted other treatment options. Clinical studies have reported that CD19 CAR T-cell therapy can lead to complete remission rates near 60% in patients with aggressive B-cell lymphomas, including DLBCL,[4] and 81% in acute B-lymphoblastic leukemia.[5] The ability of CAR T-cells to persist in the body and continue targeting cancer cells is a significant advantage over traditional therapies. In Case 1, the sustained detection of CAR T-cells for at least six months post-infusion correlated with her ongoing remission, consistent with ELIANA study,[5] suggesting that long-term monitoring of CAR T-cell persistence could be a valuable prognostic indicator.

The selection of appropriate candidates for CAR T-cell therapy is crucial. Factors such as prior treatment history, disease burden at the time of therapy, and overall health status must be carefully considered. In Cases 2 and 3, the patients had extensive treatment histories with multiple relapses, which may have contributed to their poor outcomes. Furthermore, high tumor burden of Case 3 at the time of CAR T-cell therapy also predicted the poor response.[3,5] Future studies should focus on identifying biomarkers that can predict which patients are most likely to benefit from CAR T-cell therapy while minimizing risks.

The varying severity of side effects experienced by patients highlights the importance of individualized patient management strategies. Case 1 demonstrated effective management of grade 2 CRS with timely intervention, resulting in a favorable outcome. In contrast, Case 2's severe CRS and ICANS with typical onsets led to tragic consequences, which could be related to refractory status and pre-existing neurological disorder (lymphoma and seizure), emphasizing the need for proactive monitoring and rapid response protocols, although multiple studies suggest that lymphoma CNS involvement actually does not increase the chance or severity of ICANS.[6–8] Analyses[9,10] from the ZUMA-1 cohort suggested that tocilizumab may have poor effect on ICANS. Unfortunately anakinra[11] and siltuximab[12] were not available and MMH then. Studies indicate that higher doses of CAR T-cells can increase the incidence of CRS and neurological toxicity.[13,14] Therefore, the implementation of standardized guidelines[15] for managing CRS and ICANS is essential to improve patient safety and outcomes. This includes early recognition of symptoms, appropriate use of tocilizumab and corticosteroids, and supportive care measures.

There are two CAR T-cell therapies approved by the U.S. Food and Drug Administration that are mostly used to treat lymphomas. Axicabtagene Ciloleucel (Axi-cel) and Tisagenlecleucel (Tisa-cel), each represent a distinct type of CAR T-cell therapies. Axi-cel uses CD28 as the costimulatory domain and tisa-cel 41-BB. PELL BMT doest not disclose the type of costimulatory domain. According to the review published in 2024[16] showing the real world experiences, I compared these two CAR T-cell therapies in Table 1.

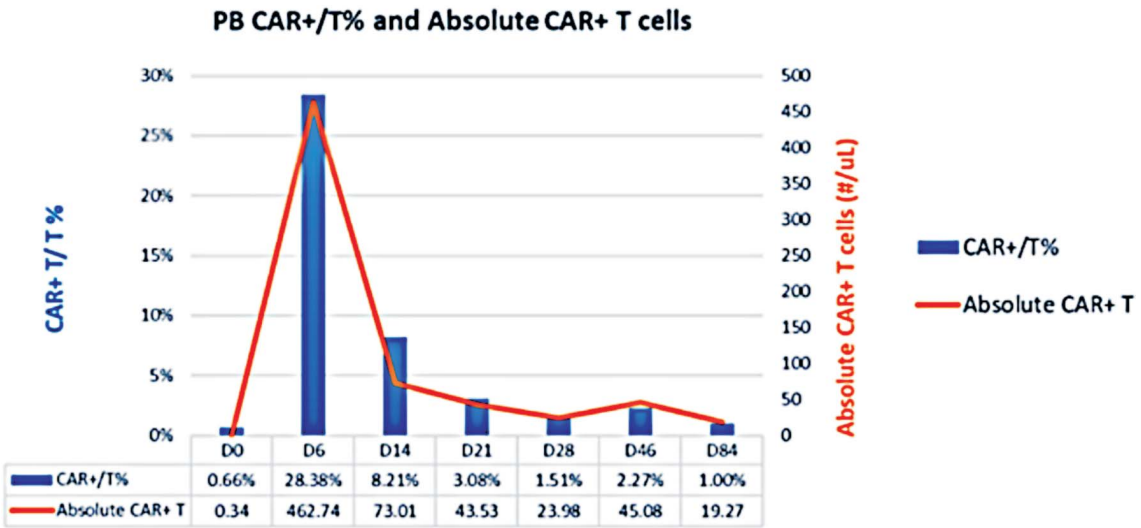

Figure 2. Dynamics of CAR T-cell in Case 3. CAR+ T/T%, the percentage of CAR T-cells among all T cells detected in the blood.

Table 1
Comparing Axi-cel and Tisa-cel.

Feature	Axi-cel Median (95% CI)	Tisa-cel Median (95% CI)	p value
Costimulatory domain	CD28	4-1BB	
Male sex	64.8 (62.9–66.6)	60.1 (58.0–62.3)	**< 0.001**
Age, yr	60.6 (59.7–61.6)	64.3 (62.8–65.8)	**< 0.001**
Median prior n lines	3.0 (2.8–3.2)	3.0 (2.6–3.5)	0.93
Prior autologous SCT	27.3 (23.6–30.9)	26.7 (22.0–31.5)	0.84
High LDH	40.6 (28.4–52.8)	42.7 (19.5–66.0)	0.84
DLBCL	73.8 (69.9–77.7)	78.6 (71.5–85.7)	0.18
GCB	52.2 (42.7–61.6)	55.2 (45.0–65.5)	0.56
PMBCL	5.2 (3.3–7.1)	.8 (-.1 to 1.8)	**< 0.001**
tFL	19.6 (17.8–21.4)	17.8 (11.8–23.8)	0.5
HGBL	14.8 (6.8–22.8)	12.0 (3.7–20.4)	0.36
Double/triple hit	17.1 (14.1–20.1)	12.0 (4.8–19.2)	**0.02**
Stage ≥ III	69.8 (63.5–76.0)	79.5 (72.1–86.8)	**0.02**
IPI ≥ 3	50.2 (46.1–54.4)	47.4 (31.6–63.2)	0.65
ECOG PS ≥ 2	9.1 (6.2–12.1)	9.1 (3.4–14.8)	1
Prior CNS involvement	2.7 (-.4 to 5.9)	0	**0.04**
CR rate	51%	39%	
Odds ratio for CR rate (95% CI)	1.7 (1.46–1.96)	Reference	
Median OS	19.5 months	11.7 months	
HR for OS (95% CI)	**0.60 (0.47–0.77)**	Reference	
Median PFS	7.3 months	3.3 months	
HR of PFS (95% CI)	**0.67 (0.57–0.78)**	Reference	
Incidence of any-grade CRS	86.30%	70.60%	
Incidence of grade ≥ 3 CRS	8.20%	8.90%	
Odds ratio of grade ≥ 3 CRS	0.94 (0.72–1.22)	Reference	
Incidence of any-grade ICANS (Neurotoxicity)	47.60%	19.90%	
Incidence of grade ≥ 3 ICANS	19%	5.80%	
Odds ratio of grade ≥ 3 ICANS	**3.95 (3.05–5.11)**	Reference	

Axi-cel may induce better overall survival, at the expense of higher ICANS.
CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal center B-cell; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplant; tFL, transformed follicular lymphoma.

Axi-cel demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to tisa-cel. This observation aligns with previous findings suggesting that CD28, as a costimulatory domain, may confer greater potency than 4-1BB, albeit potentially at the cost of an increased propensity for CRS and a significantly elevated risk of ICANS. These findings underscore the critical importance of vigilant surveillance and experienced management of ICANS when employing this more efficacious CAR T-cell therapy.

As CAR T-cell technology continues to evolve, there are promising avenues for enhancing its efficacy and safety. Research into next-generation CAR constructs or utilizing γδ-T cells aims to improve specificity and reduce side effects.[17,18] Additionally, people are exploring strategies combining CAR T-cell therapy with other modalities such as checkpoint inhibitors or targeted therapies, but so far have not seen significant benefit.[19] Furthermore, expanding access to CAR T-cell therapy through the development of off-the-shelf products could alleviate some logistical challenges associated with personalized therapies.

The exploration of alternative targets beyond CD19 may also broaden the applicability of CAR T-cell therapies to other malignancies. For instance, recent trials have shown promise in targeting B-cell maturation antigen (BCMA) for multiple myeloma patients.[3] These advancements indicate a shift towards more versatile applications of CAR T-cell technology across various hematological malignancies.

4. Conclusion

In summary, while CAR T-cell therapy represents a significant advancement in the treatment of relapsed or refractory lymphomas, it is accompanied by considerable challenges that require ongoing research and clinical vigilance. The experiences at MacKay Memorial Hospital serve as valuable lessons in understanding how to optimize patient outcomes while managing potential risks. Continued collaboration among clinicians, researchers, and regulatory bodies will be essential in refining CAR T-cell therapies and ensuring that they fulfill their promise as a cornerstone of cancer treatment.

Conflicts of interest

None.

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