Acta Haematologica Polonica 2022
Number 3, Volume 53, pages 180–182
DOI: 10.5603/AHP.a2022.0020
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

VIA MEDICA

Outpatient CAR-T therapy

Dominik Dytfeld*, Lidia Gil

Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznań, Poland

Abstract

Chimeric antigen receptor T (CAR-T) therapy has recently revolutionized the treatment of aggressive lymphomas and acute lymphoblastic leukemia, and will soon do the same for myeloma and other hematological malignancies. Due to the risk of potentially life-threatening complications such as cytokine release syndrome (CRS) and immune effector cell associated neurological syndrome (ICANS), patients have been hospitalized for the time when those symptoms may have occurred. However, due to improved prognostic factors, diagnostics and treatment of CRS and ICANS, it is possible that in the near future certain groups of patients will be treated with CAR as outpatients. That would allow broader access to CAR therapy, lowering overall costs and improving patient quality of life. Patient selection for outpatient CAR treatment is a topic that has been extensively discussed but, even based on the experience we already have, can already be effectively performed. CAR as an outpatient could be particularly useful for younger patients with a low tumor burden who have an educated caregiver and whose CAR center is logistically capable of providing outpatient care.

Key words: CAR-T, outpatient, cellular therapy

Acta Haematologica Polonica 2022; 53, 3: 180–182

Introduction

Chimeric antigen receptor T (CAR-T) therapy has recently revolutionized the treatment of aggressive lymphomas and acute lymphoblastic leukemia following the registration in 2017 of two first-in-class cellular therapies: axicabtagen ciloleucel and tisagenlecleucel. Further therapies based on CAR-T technology will soon change the landscape surrounding the treatment of myeloma and other hematological malignancies. The high effectiveness of CAR-T therapy is associated with potentially toxic complications that require hospital care. Thus, CAR-T has a significant impact on the healthcare system not only due to the costs of the procedure itself, but also due to the demands of advanced medical care which may limit the development of this fascinating and efficacious technology. Outpatient care of patients being treated with CAR therapy may become an increasingly attractive option.

Experience of outpatient care of patients after CAR therapy

There are several different CAR constructs being used in aggressive lymphomas, acute lymphoblastic leukemias, and recently in multiple myeloma. Due to different variations in CAR structure and signaling, disease entity treatment, and manufacturing differences, the frequency, severity, and timing of two very challenging complications such as cytokine release syndrome (CRS) and neurological complications (ICANS, immune effector cell associated neurotoxicity syndrome) vary between CAR agents. The anticipated timing and probability of these complications may influence outpatient treatment decisions, and can be a determining factor in making inpatient versus outpatient treatment recommendations.

There have been no prospective clinical trials comparing outpatient versus inpatient care of patients being treated

*Address for correspondence: Dominik Dytfeld, Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Szamarzewskiego 84, 60–569 Poznań, Poland, e-mail: ddytfeld@ump.edu.pl

Received: 11.04.2022 Accepted: 15.04.2022

with CAR. There are, however, some reports on outpatient treatment from published prospective clinical trials. 27% of subjects from the Juliet study were treated with tisagenlecleucel in an outpatient manner [1], while 24% were so treated in the Eliana study [2]. It is worth mentioning that a 7-day hospital stay was mandated in an axicabtagen registration study (ZUMA-1) [3]. Likewise, in three studies on lisocabtagene, a total of 59 (18%) patients were infused and observed as outpatients [4]. Patients were defined as being treated as outpatients if they were infused as an outpatient or were discharged on the same day if they had been hospitalized before the infusion. Only 17% needed to be readmitted within the first four days, and 46% did not require readmission at all. Only 3% of them were eventually admitted to the intensive care unit. Eventually patients who stayed in the hospital upfront were hospitalized for a median 15 days (range: 2–98; n = 272), while those predefined as outpatients were hospitalized for a median of only 6 (range: 2–23 days; n = 18).

In another observation reported as a single center retrospective study of 30 patients treated with tisagenlecleucel, 70% were treated fully as outpatients and only eight needed readmission, due to CRS (five) and infection (three) [5]. Outpatient care of patients treated with CAR is now being widely allowed in clinical studies like the trial of a third generation CD20 targeted CAR (consisting of both CD28 and 41BB costimulatory domains) in patients with aggressive lymphomas or in a phase III study of cilta-cell [recently Food and Druga Administration (FDA) approved B-cell maturation antigen (BCMA) targeted second generation CAR for patient with refractory multiple myeloma] in newly diagnosed multiple myeloma patients [6, 7] suggests that outpatient administration of CAR will become more common and could become the standard of care for certain populations of patients.

Why CAR outpatient?

It is apparent that CRS and ICANS management algorithms used in real-world settings have confirmed the benefit of broader and earlier use of anti-cytokine therapies such as tocilizumab and glucocorticosteroids compared to the conservative and rigorous approach reported in early clinical studies. It has been shown in real-world and clinical trials that the earlier introduction of corticosteroid and tocilizumab does not influence efficacy, although they appear to mitigate CRS intensity and the risk of ICANS. This approach is reflected in today's international guidelines and regular practice in both formally registered CARs and those being used in clinical trials [8].

The commercialization of cellular therapies, which is an obvious consequence of their unprecedented efficacy, comes alongside the need to optimize medical resources. The expanding interest in outpatient care after CAR-T is one of the major factors that may decrease cost and eventually increase access to this procedure looked at from a whole population perspective, while from the individual perspective it improves quality of life.

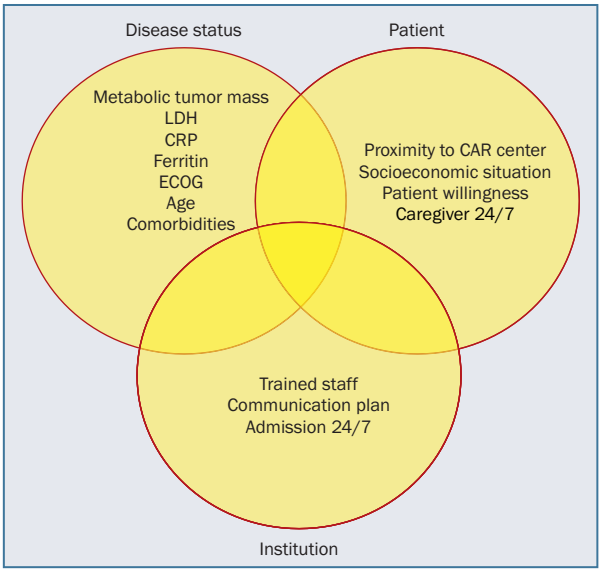

Figure 1. Conditions that need to be analyzed for outpatient chimeric antigen receptor (CAR) therapy; LDH — lactate dehydrogenase; CRP — C-reactive protein; ECOG — Eastern Cooperative Oncology Group

Such an outpatient approach certainly needs to be thoroughly thought through, taking into consideration a risk/benefit assessment, the greater predictability of clinical course, patient preference, and limited resource utilization.

Patient selection

There are several factors that have an impact on the decision as to who can be treated in an outpatient manner (Figure 1). First is the presence of sufficient logistics facilities in the CAR center, such as training classes for patients and caregivers, the 24/7 availability of medical staff for consultation, a developed communication plan within the multidisciplinary team, and the possibility of immediate admission.

The second is the ability of an individual patient and caregiver to stay near to the hospital that is capable of treating specific CAR-related toxicity. One of the most important factors is the caregiver — preferably a family member who will take care of the patient at home. The list of tasks is relatively long and consists of records of administered medications, body temperature, balance of fluids, and eventually the decision to contact medical staff when symptoms of potentially threatening complications occur. Proper patient and caregiver education on the complications that require immediate intervention is key for safe outpatient CAR therapy.

However, the most critical factors are those related to the probability, severity and time to onset of CRS and ICANS. Factors predicting severe CAR-related toxicity that might be contraindications for an outpatient approach are: activity of preinfusion lactate dehydrogenase, preinfusion C reactive protein and ferritin levels, metabolic tumor volume, comorbidities, age and Eastern Cooperative Oncology Group (ECOG) performance status [9], although these factors are not finally conclusive and longer observations need to be performed to create a clear algorithm in the inpatient/outpatient decision process.

Care after CAR infusion

Care given by the non-medical caregiver is important for successful and safe treatment with CAR therapy, although contact with trained medical staff is essential. There are several, slightly different, recommendations on how often and for how long a patient after CAR infusion should be seen by medical professionals. According to the Risk Evaluation and Mitigation Strategy (REMS) developed for tisagenlecleucel, the patient should remain for one month within two hours of the CAR center. Similar recommendations have been created for other CAR products. In an outpatient approach, the patient should visit the CAR center every day during the first week and 2–3 times in the second week to access potential complications in both clinical and laboratory aspects. Close contact is needed especially in the first week with readiness for admission if any severe or potentially severe complication occurs [9]. Additionally, patients and caregivers should have a wallet card setting out how to contact healthcare providers in life-threatening situations.

Patients should be readmitted when there is a fever suggestive of CRS, especially in coexistence with neutropenia. Any other clinical or laboratory symptom of infection should be used as an argument for readmission. Any patient with psychiatric or neurological abnormalities should also be considered for readmission.

Conclusions

CAR therapy is an emerging new standard of care in patients treated due to aggressive lymphomas, acute lymphoblastic leukemias, and (soon) multiple myelomas. Due to the high costs and the need to conduct therapy only in accredited centers, a possibility of outpatient care of patients after CAR therapy is an attractive option that will eventually increase access to cellular therapies. The determination of predictive factors of severity and time of onset of CAR-related toxicities and the optimization of supportive care and treatment of CRS and ICANS will identify patients who can be effectively and safely treated in an outpatient manner that eventually will become the standard of care.

Authors' contributions

DD, LG — wrote the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Financial support

The authors declare no financial support for this work.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References

1. Schuster SJ, Tam CS, Borchmann P, et al. JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019; 380(1): 45–56, doi: 10.1056/NEJMoa1804980, indexed in Pubmed: 30501490.
2. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018; 378(5): 439–448, doi: 10.1056/NEJMoa1709866, indexed in Pubmed: 29385370.
3. Locke FL, Ghobadi A, Jacobson CA, 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. Lancet Oncol. 2019; 20(1): 31–42, doi: 10.1016/S1470-2045(18)30864-7, indexed in Pubmed: 30518502.
4. Bachier CR, Godwin J, Andreadis C, et al. Outpatient treatment with lisocabtagene maraleucel (liso-cel) across a variety of clinical sites from three ongoing clinical studies in relapsed/refractory (R/R) large B-cell lymphoma (LBCL). J Clin Oncol . 2020; 38(15_suppl): 8037–8037, doi: 10.1200/jco.2020.38.15_suppl.8037.
5. Dwivedy Nasta S, Namoglu EC, Hughes ME, et al. Hospitalization patterns with commercial CAR T-cell therapy: a single institution experience. Blood. 2019; 134(Suppl_1): 3240, doi: 10.1182/blood-2019-130650.
6. Shadman M, Gopal A, Smith S, et al. CD20 targeted CAR-T for high-risk B-cell non-Hodgkin lymphomas. Blood. 2019; 134(Suppl_1): 3235, doi: 10.1182/blood-2019-125102.
7. Dytfeld D, Dhakal B, Agha M, et al. Bortezomib, lenalidomide and dexamethasone (VRd) followed by ciltacabtagene autoleucel versus VRD followed by lenalidomide and dexamethasone (Rd) maintenance in patients with newly diagnosed multiple myeloma not intended for transplant: a randomized, phase 3 study (CARTITUDE-5). Blood. 2021; 138(Suppl 1): 1835, doi: 10.1182/blood-2021-146210.
8. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022; 33(3): 259–275, doi: 10.1016/j.annonc.2021.12.003, indexed in Pubmed: 34923107.
9. Myers GD, Verneris MR, Goy A, et al. Perspectives on outpatient administration of CAR-T cell therapy in aggressive B-cell lymphoma and acute lymphoblastic leukemia. J Immunother Cancer. 2021; 9(4), doi: 10.1136/jitc-2020-002056, indexed in Pubmed: 33846220.