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Perspectives on outpatient administration of CAR-T cell therapy in aggressive B-cell lymphoma and acute lymphoblastic leukemia

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ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapies that specifically target the CD19 antigen have emerged as a highly effective treatment option in patients with refractory B-cell hematological malignancies. Safety and efficacy outcomes from the pivotal prospective clinical trials of axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel and the retrospective, postmarketing, real-world analyses have confirmed high response rates and durable remissions in patients who had failed multiple lines of therapy and had no meaningful treatment options. Although initially administered in the inpatient setting, there has been a growing interest in delivering CAR-T cell therapy in the outpatient setting; however, this has not been adopted as standard clinical practice for multiple reasons, including logistic and reimbursement issues. CAR-T cell therapy requires a multidisciplinary approach and coordination, particularly if given in an outpatient setting. The ability to monitor patients closely is necessary and proper protocols must be established to respond to clinical changes to ensure efficient, effective and rapid evaluation either in the clinic or emergency department for management decisions regarding fever, sepsis, cytokine release syndrome and neurological events, specifically immune effector cell-associated neurotoxicity syndrome. This review presents the authors' institutional experience with the preparation and delivery of outpatient CD19-directed CAR-T cell therapy.

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy involves the genetic engineering of a patient's own T cells to express CARs that are engineered to target specific epitopes of tumor-associated antigens expressed on the target cell surface.[1] The aim of current CAR-T cell therapy is the redirection of cellular cytotoxicity to malignant cells. Immune effector cell toxicities may vary between different agents, such as tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel and most recently brexucabtagene autoleucel, based on variations in CAR structure and signaling, disease entity treated and manufacturing differences. These variations may affect the time to emergence and severity of complications and factor into adopting inpatient versus outpatient CAR administration (box 1).[2 3]

Tisagenlecleucel is approved for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse.[4] Tisagenlecleucel and axicabtagene ciloleucel are both approved for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma (HGBCL) and transformed DLBCL (tDLBCL) arising from follicular lymphoma (FL).[4 5] Axicabtagene ciloleucel is also approved for treatment of patients with r/r primary mediastinal large B-cell lymphoma (PMBCL).[5] Lisocabtagene maraleucel is a CAR-T cell therapy tested in patients with DLBCL and was recently approved (February 5, 2021) by the US Food and Drug Administration. Brexucabtagene autoleucel is a recently approved CAR-T product for relapsed or refractory mantle cell lymphoma (online supplemental table 1). This review presents the authors' institutional approach to and experience with outpatient administration of CD19-directed CAR-T cell therapy in adult patients with r/r DLBCL. Outpatient administration of CAR-T cell therapy in pediatric and young adult patients with r/r B-ALL is also discussed.

CAR-T CELL THERAPY EFFICACY

Clinical trials in patients with r/r DLBCL

Clinical trials of CAR-T cell therapies have demonstrated high response rates that are durable in patients with r/r DLBCL (online supplemental table 2). The pivotal ZUMA-1

Box 1 Recommendations for outpatient infusion of CAR-T cell therapy

Preinfusion

- Consider the patient's predicted time to onset of CRS and NE (ie, early vs late).
- Evaluate the patient's degree of socioeconomic support, including the level of social/familial support, as assessed by social work services.
- Consider feasibility of an individual infusion room.
- Confirm patient's possession of the wallet card for instructions concerning potential complications.
- Communicate with the manufacturing facility to ensure that manufacturing will be completed and the product will be shipped at the appropriate time.
- Instruct the patient to remain within a 1-hour transportation distance from the outpatient center for at least 4 weeks postinfusion.[a]
- Complete COVID-19 testing prior to infusion.

Postinfusion

- Monitor the patient at the certified healthcare facility frequently during the first week for signs and symptoms of CRS and ICANS, tumor lysis syndrome and cytopenias.
- Continue prophylactic treatment with antibiotics and other supportive care.
- Ensure communication with on-call oncology and emergency department teams concerning the patient's treatment with CAR-T cell therapy.
- Consider hospital admission if:
  - The patient develops a fever (≥38°C).
  - Fever is present in a patient with a high predicted risk for progression to severe complications (eg, high baseline tumor burden).
- For discharge after admission, consider timing of fever resolution from CAR-T infusion, presence/absence of documented infections and neutrophil recovery.

[a]Patients considered 'high risk' due to tumor bulk >10 cm. Nastoupil,[2] high lactate dehydrogenase[3] and multiple preexisting medical comorbidities, for example, are commonly instructed to remain within a 30 min transportation distance; if possible, it is preferable for patients to be housed in close proximity to the institution.

CAR-T, chimeric antigen receptor T-cell; CRS, cytokine relsease syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NE, neurological events.

trial (NCT02348216) is a phase 2, single-arm study of axicabtagene ciloleucel in patients with DLBCL, transformed FL (tFL) or PMBCL.[6] The pivotal JULIET trial (NCT02445248) is a phase 2, single-arm study of tisagenlecleucel in patients with r/r DLBCL or tFL.[3] Lastly, the phase 1 TRANSCEND-NHL-001 trial (NCT02631044) enrolled patients with DLBCL, tFL, FL grade 3B, HGBCL, mantle cell lymphoma, PMBCL or tDLBCL.[7] Of note, in ZUMA-1 all patients had refractory disease (according to SCHOLAR-1 criteria) and bridging chemotherapy was not permitted, whereas JULIET and TRANSCEND-NHL-001 included patients with r/r disease and the option for bridging chemotherapy (used in 90% and 59% of patients, respectively).

Postmarketing experience of CAR-T cell therapy in patients with r/r DLBCL

Several multicenter retrospective analyses have examined patient and disease characteristics, clinical outcomes and complications using postapproval data from the Center for International Blood and Marrow Transplant Research Cellular Therapy Registry, the US CAR-T Cell Consortium, and institutions using commercially available CAR-T cell therapies. Demographics and baseline disease characteristics for patients included in these descriptive retrospective analyses of tisagenlecleucel and axicabtagene ciloleucel show significant drift from the restrictive eligiblity of the clinical trials.[2 8–11] Despite an older, broader patient population with more comorbidities in the postapproval setting (>50% of patients would not have qualified based on ZUMA-1 eligibility criteria[12]), efficacy outcomes similar to those observed in clinical trials for both CAR-T cell therapies were reported across treatment settings (online supplemental tables 2–3).[2 8 10]

Clinical trial and postmarketing experience of CAR-T cell therapy in patients with r/r B-ALL

Currently, tisagenlecleucel is the only CAR-T cell therapy approved in pediatric and young adult patients with r/r B-ALL. The ELIANA clinical trial is a phase 2, multicenter, global study of tisagenlecleucel in children and young adults with r/r B-ALL (NCT02435849).[13] The real-world data in a similar patient population confirms the efficacy findings from the ELIANA trial, and more favorable safety findings compared with the ELIANA trial support the benefit of CAR-T cell therapy in pediatric and young adult patients with r/r B-ALL (online supplemental tables 2–3). Additionally, this experience may suggest that lessons from the clinical trial, as well as enhanced manufacturing capability,[14] may be translated into an improved safety profile for tisagenlecleucel in pediatric and young adult patients with r/r B-ALL.

CAR-T CELL THERAPY SAFETY

These groundbreaking effector cell-based therapies have revealed novel toxicities not previously seen with other anticancer therapies, including potentially life-threatening events such as cytokine release syndrome (CRS) and neurological events (NE), particularly immune effector cell-associated neurotoxicity syndrome (ICANS; online supplemental tables 2–3). Considering the differences in grading and management of CRS and NE,[15–22] in addition to new learnings that have changed practices over time, it can be challenging to use the current reported trial data to assess patient risk and suitability for outpatient CAR-T cell therapy administration. The anticipated timing and probability of these complications may influence outpatient treatment decisions and be a determining factor in the inpatient versus outpatient treatment recommendation. In addition, the authors are not aware of any published randomized data demonstrating differential efficacy or safety for tisagenlecleucel or lisocabtagene maraleucel

administered in the outpatient versus inpatient setting, suggesting that clinical outcomes are not affected by the inpatient versus outpatient treatment decision. However, 26% of patients received outpatient treatment in JULIET; of those admitted, many were discharged after a limited observation period. In contrast, a 7-day hospital stay was mandated in ZUMA-1.[6]

The 4 CAR-T cell therapies differ in their cosignaling molecule/activation domains: the CD28 activation domain within axicabtagene ciloleucel and brexucabtagene autoleucel is believed to amplify early CAR-T cell expansion postinfusion,[23] and the 4-1BB activation domain within the tisagenlecleucel and lisocabtagene maraleucel CARs is believed to confer slower expansion and prolonged CAR-T cell persistence.[24] Compared with the CD28 activation domain containing axicabtagene ciloleucel, the later onset of CRS observed in clinical trials with the 4-1BB activation domain CARs tisagenlecleucel and lisocabtagene maraleucel have facilitated adoption of outpatient administration of these therapies (online supplemental table 2).[25] It is apparent that CRS and NE management strategies used in the real-world setting have confirmed the benefit of increased and earlier use of tocilizumab and corticosteroids for CRS and NE compared with the standard algorithms used in clinical trials, and these medications are now recommended in recent management guidelines.[16 19 26] Early clinical trials of CAR-T cell therapies have used the Common Terminology Criteria for Adverse Events to define NE, which include vague, overlapping, subjective terms that may not be clinically relevant to management of CAR-T cell therapy-induced NE. In comparison, ICANS defines the adverse events resulting from T-cell effects on the central nervous system (CNS), which can result from immune therapies, including CAR-T cell therapy. Management strategies used in the real-world setting have also evolved to better characterize ICANS.[7 8 10 11 27–30] Overall, real-world and clinical trial data suggest that earlier corticosteroid and tocilizumab use does not influence efficacy, although they appear to mitigate CRS intensity.

OUTPATIENT PREPARATION AND INFUSION

Procedural considerations for the multidisciplinary team that administers CAR-T cell therapy and manages patients before, during and after CAR-T cell infusion apply to both the inpatient and outpatient settings, including limitation of precollection treatments that could induce subsequent CAR-T cell dysfunction, addressing the timing of apheresis, disease status, clinical laboratory testing and the use of bridging and lymphodepleting chemotherapy.[4 5]

For outpatient infusion of tisagenlecleucel, an individual infusion room, rather than an open-air infusion chair, is preferred given the need for monitoring and the potential for infusion reactions, similar to situations for outpatient autologous transplantation. However, the small volume and number of thawed cryopreserved CAR-T cells make this a rare event. Similar monitoring is needed for administration of lisocabtagene maraleucel, but it is important to note that the independent CD4 and CD8 components are administered by direct 'slow' intravenous push and with a defined constituent administration order of the CD4 and CD8 fractions.[31]

INPATIENT VERSUS OUTPATIENT INFUSION

With commercialization, there is continually expanding interest in administering all CAR-T cell therapies in the outpatient treatment setting based on a risk–benefit assessment, greater predictability of clinical course, patient preference, limiting resource utilization and controlling reimbursement uncertainty. Although CAR-T cell therapies can be administered safely in the outpatient setting, most patients still receive treatment in an inpatient setting. The choice of outpatient administration of CAR-T cell therapy is influenced by several factors. First, specific institutional training and safeguards must be implemented prior to outpatient administration, including education of the patient, physician (including on-call physicians), the infusion center and emergency department personnel. Second, covering practice providers should be alerted that an outpatient has been infused with CAR-T cell therapy and could experience complications requiring early intervention. Third, better understanding of predictive risk factors for the likelihood of CRS development can influence the decision of whether to pursue outpatient infusion. Variation in reimbursement policies, including whether patients have public or private insurance, has had drastic implications for institutions, payers and patients. Additionally, adequate caregiver education and support is key for safe outpatient administration. Finally, in response to the COVID-19 pandemic, commercial CAR-T cell therapy has been administered in the inpatient setting to ensure bed availability in case complications were encountered. Despite the perceived hurdles associated with outpatient administration of CAR-T cell therapy, growing real-world experience, including the ability to modulate disease burden and timing of CAR-T cell infusion, supports the safe delivery of CAR-T cell therapy in the outpatient setting. In fact, the capability of patients to return to the hospital for fever may influence the decision to infuse and monitor in the inpatient setting to a greater extent compared with these other factors.

Feasibility of outpatient administration

The feasibility of outpatient administration (including infusion, patient monitoring and adverse event management) in the clinical trial setting has been shown in patients in the JULIET and TRANSCEND (r/r DLBCL) and ELIANA (r/r ALL) trials.[32–34] In the JULIET trial, 27% of patients were infused in the outpatient setting.[4] In the ELIANA trial, 24% of patients received their infusions in the outpatient setting.[33] A total of 59 patients (18%) were treated with lisocabtagene maraleucel in the outpatient setting from three clinical trials with

lisocabtagene maraleucel: TRANSCEND (9% treated as outpatient), and two investigational ongoing trials for treatment of r/r DLBCL with lisocabtagene maraleucel as second-line therapy (41% treated as outpatient; PILOT, NCT03483103) and third-line or later therapy (65% treated as outpatient; OUTREACH, NCT03744676).[35] Patients were considered outpatients if they received lisocabtagene maraleucel infusion in the outpatient or inpatient setting and then left the clinic or were discharged from the hospital on the day of infusion. Eighty-three per cent of patients who received lisocabtagene maraleucel in the outpatient setting did not require hospitalization within the first 4 days after infusion, and 46% did not require any hospitalization after infusion. Intensive care unit (ICU)-level care was ultimately required in 3% of patients who received outpatient infusions. The median number of days of hospitalization following lisocabtagene maraleucel infusion for inpatient infusion was 15 days (range, 2–98 days; n=272) compared with 6 days (range, 2–23 days; n=18) for outpatients. Among patients in the TRANSCEND trial who received lisocabtagene maraleucel in the outpatient setting and then were admitted (n=18), the median time to hospitalization was 5 days (range, 3–22 days), 6 patients (24%) were hospitalized on day 4 or earlier, and 1 patient (4%) required ICU admission. Overall, patients who received lisocabtagene maraleucel infusion in the outpatient setting required less hospitalization time compared with those who were infused in the inpatient setting. This was likely driven by patient-specific factors, such as disease burden. However, a reduction in hospital admission days with outpatient CAR-T infusion may be more convenient and preferred by patients and health systems where this can be safely performed.

Tisagenlecleucel administration in the outpatient setting has also been recently demonstrated in 30 patients with non-Hodgkin's lymphoma (NHL) from a single-center, retrospective study.[36] Following outpatient infusion, 70% were managed entirely as outpatients. Of the 30% of patients admitted within the first 30 days after infusion, most admissions were due to fever (89%; n=8) resulting from CRS (63%; n=5) and infection (38%; n=3).

Outpatient administration is also being used in a clinical trial of a third-generation CAR-T cell therapy. MB-106, a fully humanized, third-generation, CD20-targeted CAR-T cell therapy that includes both the 4-1BB and CD28 costimulatory domains, will be administered in the outpatient setting in nearly all patients with NHL in this single-center study.[37] These observations suggest that outpatient administration is becoming standard practice as clinicians become familiar with safely infusing CAR-T cell therapy in this setting; however, there exists important patient-related considerations, aside from the infusion procedure itself, that may be a barrier to outpatient administration (see next section).

Considerations for the outpatient administration decision

Patient-specific factors must be assessed for inpatient versus outpatient administration. In clinical practice with tisagenlecleucel, physician preference for outpatient administration will depend on the available institutional resources (eg, training classes for the patient and caregiver and support for a 24-hour consultation to evaluate CAR-T cell therapy-related toxicity), the feasibility of the patient remaining within close proximity to the center, and the level of caregiver support. The primary considerations for determining individual patient suitability for outpatient administration are often the probability, severity, and the predicted time to onset (ie, early vs late) of CRS and ICANS, as well as the availability of socioeconomic support (ie, assessed willingness, understanding and ability to return to the medical center with concerning signs and symptoms). Outpatient administration might be considered if a patient's disease burden is low. In this case, lower rates and delayed onset of CRS are expected, allowing the patient to safely leave the infusion center while still vigilantly monitoring for symptoms of CRS. Alternatively, if disease burden is high (tumor bulk >10 cm and/or increased positron emission tomography (PET) metabolic tumor volume[38]) or is driving active fevers and/or febrile neutropenia, assignment to inpatient administration may be preferred because the onset of CRS will likely be rapid and CRS may be severe, requiring immediate intervention by the multidisciplinary team. Emerging factors associated with increased incidence or greater severity of CRS and/or NE, include elevated preinfusion lactate dehydrogenase, metabolic tumor volume, Eastern Cooperative Oncology Group performance status, and preinfusion C reactive protein and ferritin levels.[2 3 30 39–43] Although consideration of these factors is important for predicting safety outcomes, these factors are not 100% predictive.

Among patients with NHL, potentially complicating patient-related and disease-related factors, including secondary CNS disease, multiple comorbidities and age (≥65 years), do not preclude treatment with CAR-T cell therapy.[10 44–47] For example, in a single-center, retrospective analysis of 8 patients with active secondary CNS lymphoma who received tisagenlecleucel therapy, no patient experienced >1 event of grade 1 NE.[45] Similarly, findings from the US Lymphoma CAR-T Consortium demonstrated comparable rates of axicabtagene ciloleucel infusion, efficacy and safety outcomes in patients with secondary CNS disease compared with patients without CNS disease.[44] As such, outpatient administration for these otherwise clinically challenging patients should be considered because risk of complications is not increased in these patient populations.

The patient's level of social/familial support is another key factor to consider. Outpatient administration requires around-the-clock caregiver support during treatment and involves responsibility for a variety of tasks.[48] For example, caregivers are commonly asked to keep a written record of when medications are administered, the patient's body temperature, and the amount of fluids consumed; understand the signs and symptoms of potential complications for which to seek immediate medical

attention; provide transportation to and from hospital visits; maintain cleanliness at home; manage the number of in-home visitors to minimize the patient's risk of exposure to anyone who is sick; communicate with and listen to the patient; and understand the patient's needs and decisions.[48] Thus, the potential for social/familial challenges associated with the caregiver's ability to support day-to-day medical needs, practical considerations and emotional needs should be evaluated when considering outpatient treatment.The outpatient social work service performs a critical role by providing non-medical assessments to help guide the outpatient treatment decision. On occasion, DLBCL patients are not treated with CAR-T cell therapy following these assessments.[49] For pediatric patients with ALL who lack social/familial support, treatment with CAR-T cell therapy is typically administered in the inpatient setting. Outpatient administration of CAR-T cell therapy should be considered on a patient-by-patient basis along with the practical and institutional conditions presented herein.

POSTINFUSION MONITORING AND PATIENT FOLLOW-UP

Patients who receive tisagenlecleucel are generally instructed to remain within a 1-hour transportation distance from the outpatient center for at least 4 weeks postinfusion for treatment of potential emergent procedural complications[4]; the Risk Evaluation and Mitigation Strategy (REMS) for tisagenlecleucel indicates that patients should plan to remain within 2 hours of the outpatient center for at least 4 weeks. Similarly, patients who received lisocabtagene maraleucel in TRANSCEND-NHL-001 were instructed to remain within a 1-hour transportation distance for 30 days.[32] Patients considered 'high risk' due to tumor bulk >10 cm, high lactate dehydrogenase or multiple preexisting medical comorbidities, for example, are commonly instructed to remain within a 30 min transportation distance; if possible, it is preferable for patients to be housed in close proximity to the institution. Institutions may provide travel and lodging assistance through support from insurance companies or CAR-T cell therapy manufacturers for patients residing within a 30–60 min transportation distance from the treatment center.[50] The outpatient approach is for patients to be monitored at the Foundation for the Accreditation of Cellular Therapy-accredited facility with 2–3 and sometimes daily visits during the first week following infusion to monitor for CRS and ICANS, in addition to laboratory monitoring for tumor lysis syndrome or cytopenias. During the second week, patients are monitored 2–4 times, then two times per week for the following 2 weeks. With this approach, outpatient administration of CAR-T cell therapy can be successful, but critical to this effort is the awareness of the variation in median time to CRS between CAR-T cell therapies. Close contact is needed throughout the first week with the CAR-T medical team, and rapid conversion to the 24-hour monitored setting is required if an observation or inpatient ward is needed for CRS or other medical events. Outpatient administration should be considered whenever feasible to reduce inpatient healthcare utilization during the COVID-19 pandemic; however, outpatient administration may not be practical due to institutional resources and viral burden in the surrounding community.[51]

Per industry and US Food and Drug Administration (FDA) guidelines, including REMS, before receiving treatment with FDA-approved CAR-T cell products axicabtagene ciloleucel and tisagenlecleucel, patients and caregivers must be provided with a patient wallet card that advises on the signs and symptoms of CRS and instructs when and how to contact the patient's healthcare provider. The patient wallet card also includes directions for healthcare providers to consult the patient's treating oncologist if the patient requires steroids or cytotoxic medications, requires an invasive procedure, or has a serious infection.

Considerations for hospital admission

The decision of when to admit patients following outpatient CAR-T cell infusion is a key consideration and may vary across treatment centers. Typically, the patient or caregiver contacts the treatment center to report fever. The decision to admit the patient may vary according to the patient's predicted risk for progression to severe complications (eg, high baseline tumor burden)[40 42 52 53]; however, patients with low disease burden are often admitted. Based on the authors' clinical experience, patients who receive tisagenlecleucel in the outpatient setting are admitted for observation and/or into the inpatient hospital ward if they develop a fever (defined as ≥38°C) due to the potential for rapid progression of CRS and to evaluate for and treat infectious etiologies and sepsis. The majority of patients with fever are admitted, particularly if fever occurs within 28 days postinfusion, if the patient is neutropenic, and/or if institutional logistical complications are evident. Occasionally, with a single fever (<38°C and/or fever that dissipates with hemodynamic stability), the decision to admit is based on clinical course. The authors stress consideration of typical complications of chemotherapy, such as bacteremia and sepsis, and thus recommend empiric antibiotic use on admission for fever. Although infection prophylaxis is not required prior to infusion, local guidelines for infection prophylaxis based on the degree of preceding immunosuppression can be considered. When CAR-T cell therapy is administered in the outpatient setting, it is also important for patients and caregivers to be educated about the signs and symptoms of infections. If a patient is readmitted for suspected infection, symptom-directed broad-spectrum antibiotics should be administered.[54] For patients who receive tisagenlecleucel in the outpatient setting, CRS is diagnosed based on clinical signs and symptoms, such as fever, hypoxia or hypotension.[15–17]

One unresolved issue is the criteria for hospital discharge to the outpatient setting. Considerations include timing of fever resolution from CAR-T cell infusion, presence/

absence of documented infections and neutrophil status. Counterbalancing the above with prolonged cytopenias that are sometimes associated with CAR-T cell therapy can be challenging. Additionally, myeloid growth factors, such as granulocyte colony-stimulating factor (G-CSF), traditionally have not been used early during the clinical testing of these products due to the theoretical risk of exacerbating CRS. However, investigators have begun to incorporate their use, with no clarity on start dates, but generally no sooner than day 21–28 postinfusion. In patients who experienced life-threatening infections, the authors have safely used G-CSF as early as 2 weeks after infusion. Care must be used to balance risks and benefits of G-CSF during expanded commercial use of CAR-T cell therapy in different clinical situations.

Coordination of multidisciplinary care is crucial for treatment with CAR-T cell therapies in the outpatient setting, particularly among on-call oncology teams. Clinical, emergency department and any other on-call personnel at the treatment facility must be made aware that the patient has received treatment with CAR-T cell therapy, as they may be the point of first contact and their center may manage complications. On-call services must appropriately route patients and recognize that patients who have received CAR-T cell therapy may have a lower threshold for fever admission compared with other oncology patients. Factors to consider before and after outpatient administration are summarized in box 1.[2 3] Additionally, recommendations for infection prevention in these patients have recently been published.[54]

FINANCIAL IMPLICATIONS OF OUTPATIENT TREATMENT

Even though the cost of CAR-T cell therapies is high, there is potential for reductions in these costs, and cost-effectiveness profiles of CAR-T cell therapies should be placed in the context of standard-of-care options. For instance, administering CAR-T cell therapy to all indicated patients with r/r DLBCL would increase US healthcare costs by approximately US$10 billion over 5 years.[55] Additionally, when tisagenlecleucel and axicabtagene ciloleucel were each compared with salvage chemoimmunotherapy regimens and stem cell transplantation, both therapies achieved a less than US$150 000 per quality-adjusted life-years thresholds solitary, potentially curative therapy with greatest benefit predicted for young patients with ALL.[55 56] In pediatric and young adult r/r B-ALL, CAR-T cell therapy increased the total cost of treatment by US$528 200 compared with standard-of-care chemotherapy, but increased effectiveness by 8.18 quality-adjusted life-years.[57] Currently, commercial CAR-T cell therapy for r/r ALL is limited to patients ≤25 years of age.[4] Early adult ALL studies were delayed due to perceived toxicity and only now are reemerging as targets for future clinical trials. Accordingly, allogeneic transplantation offers the only opportunity for cure in these older ALL patients, and there remains no meaningful therapy for patients who relapse after transplantation or those who have refractory disease. Thus, despite their costs, CAR-T cell therapies have an acceptable cost-effectiveness profile and, with ongoing improvements in manufacture, are anticipated to further improve.

Variations in reimbursement policies in the USA based on whether patients have public or private insurance and whether they are infused in the inpatient or outpatient setting have significant implications for institutions, payers and patients.[58] For patients with private insurance, often self-funded plans supported by their employer, preauthorization negotiations are the standard, whereby drug reimbursement is frequently approved. However, with governmental coverage (Centers for Medicare and Medicaid Services; CMS), reimbursement is based on the services provided based on a diagnostic code. Inpatient reimbursement is based on a bundled charge, linked to a diagnosis-related group (DRG) code, which is meant to standardize prospective payments for an inpatient stay. In the outpatient setting, reimbursement for services is based on an ambulatory payment classification that bills for daily services and is typically shared by the governmental payer and the patient copay. For CAR-T cell therapy in the outpatient setting, institutions are allowed to bill Medicare the average sales price +6%,[59] which leads to full cost reimbursement for the CAR-T cell product. CMS made a change to its policy early on that impacts the copayment for patients receiving CAR-T cell therapy in the outpatient setting in a positive way: the outpatient drug copayment for patients receiving CAR-T cell therapy is capped at the inpatient deductible amount of US$1408 (2020 rate).[60] Normally, patients receiving drugs in the outpatient setting have a 20% copayment.[60] The financial responsibility of 20% of the current list price of the commercially available CAR-T cell therapies would be unmanageable for nearly all patients.

The inpatient situation is different and currently is under great scrutiny and significant evolution. Using current CMS guidelines, the center receives a DRG code bundled payment based on the rate associated with autologous stem cell transplantation (MS-DRG 016), which is approximately 10-fold less than the cost of CAR-T cell therapy. There have been some adjustments to make up the difference, including the previous granting of new technology add-on payments that cover up to 65% of the cost of drug acquisition up to a maximum amount based on total billed charges and the hospital's overall cost-to-charge ratio (CCR).[61] However, as of September 30, 2020, the NTAP was eliminated with the new CMS proposed schedule[61] and replaced by a new diagnostic code: MS-DRG 018, CAR T-cell Immunotherapy. The proposed unadjusted reimbursement rate of approximately US$239 400 appears to be a considerable improvement for hospital systems over the previous rate of approximately US$43 100 when inpatient CAR-T cell therapy services were part of MS-DRG 016.[62] In addition, outlier payments may reimburse a significant percentage of the remaining costs. Yet, inpatient coverage rates will still be predicted to remain below hospitals' costs.

Table 1 Considerations for outpatient infusion of CAR-T cell therapy

Factor category	Factor to be assessed	Specific considerations
Disease/clinical	Preinfusion LDH*	▶ Subgroups defined for tisagenlecleucel: normal/low; high: 1–2×ULN, high: over 2×ULN†; subgroups as defined for lisocabtagene maraleucel: > or <500 U/L.‡
	Metabolic tumor volume*	▶ Patients considered high-risk due to tumor bulk >10 cm.§
	Preinfusion CRP*	▶ High CRP was associated with worse OS, but not PFS, in univariate Cox regression analysis.† ▶ High CRP associated with CRS and NE, and is lower in patients with durable response.‡
	Preinfusion ferritin*	▶ High ferritin was associated with worse OS, but not PFS, in univariate Cox regression analyses.† ▶ High CRP associated with CRS and NE, and is lower in patients with durable response.‡
	ECOG PS*	▶ ECOG PS 2–4 was associated with inferior outcomes.¶
	Presence of secondary CNS disease, multiple comorbidities and age ≥65 years	▶ Outpatient administration for these otherwise clinically challenging patients should be considered since risk of complications is not increased in these patient populations.**, ††, ‡‡, §§, ¶¶
	Disease burden	▶ Outpatient administration may not be suitable for patients with serious concurrent infection (eg, invasive fungal disease) or presence of cytopenias with fever.
Patient	Capability of patients to return to the hospital for fever	▶ Willingness, understanding and ability to return to the medical center with concerning signs and symptoms.
	Socioeconomic support	
	Patient's proximity to the treating institution	
	Patient's preference for outpatient versus inpatient infusion	▶ Outpatient therapy allows a return to 'normalcy'.
	Reimbursement policies	▶ Coverage variation between insurance types. – Private—reimbursement is frequently approved. – Public—reimbursement is based on the services provided, which vary between inpatient and outpatient infusion. ▶ Reimbursement implications need to be clarified/improved. ▶ Variation concerning whether outpatient treatment will be beneficial to both patients and institution. ▶ Rules for reimbursement are constantly evolving.
Institutional	Multidisciplinary team training	▶ Proper institutional training and safeguards for the patient, physician (including on-call physicians), the infusion center and emergency department personnel.
	Multidisciplinary team communication plan	▶ Communication with clinical, emergency department and any other on-call personnel at the treatment facility. – May be the point of first contact to manage adverse events.
	Reimbursement policies	▶ Institutions are better positioned to avoid losses with outpatient infusion (overall cost-to-charge ratio, degree of price markups, option for outlier payments). ▶ Reimbursement implications need to be clarified/improved. ▶ Variation concerning whether outpatient treatment will be beneficial to both patients and institution.

Although consideration of these factors is important for predicting safety outcomes, these factors are not 100% predictive.
*Associations with elevated level/scores and increased incidence or greater severity of CRS and/or NE have beed reported.
†Westin *et al*.[3]
‡Siddiqi *et al*.[42]
§Nastoupil *et al*.[2]
¶Jacobson *et al*.[39]
**Pasquini *et al*.[10]
††Bennani *et al*.[44]
‡‡Frigault *et al*.[45]
§§Kilgore *et al*.[46]
¶¶Kittai *et al*.[47]
CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; CRP, C reactive protein; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NE, neurological events; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

In order for hospitals to manage the financial impact of offering CAR-T cell therapy, price markups should be carefully considered. Payment is dependent on the total billed charges for the case and the hospital's CCR. The unadjusted payment represents the payment amount before the hospital's CCR is applied by Medicare for calculating the final payment. If the hospital charge for the CAR-T cell product is set too low, the result will be reimbursement from CMS that does not cover the full hospital costs. If the charge is set too high, consumers and industry watchdogs may raise concern, recognizing that CAR-T cell therapy charges are publicly posted. In addition, there are a small number of US cancer-focused institutions that are exempt from the standard rules of DRG reimbursement, and many CAR-T cell therapy patients have been treated in these institutions, thus creating a blend of patient claims from which the estimated average reimbursement must be based. With all these considerations, institutions are better positioned to avoid cost losses with outpatient administration of CAR-T cell therapy.

It is critical to be aware that if CAR-T cell therapy is administered in the outpatient setting and a patient is admitted within 3 days of infusion, Medicare applies all charges incurred for the previous 72 hours to the inpatient stay with its lower inpatient rate.[58] Thus, reimbursement

depends on maintaining patient outpatient status as long as possible. An economic model developed to assess the total costs associated with tisagenlecleucel treatment among adult patients with r/r DLBCL in the USA found that the proportion of costs for inpatient and ICU admission not attributed to the management of adverse events accounted for US$24 285 (37.5%) of the total cost of care associated with the tisagenlecleucel treatment.[63] For r/r B-ALL, the inpatient ICU costs not attributing to adverse events accounted for 42.1% of the total cost of care after tisagenlecleucel.[64] Thus, outpatient administration of CAR-T cell therapy would minimize costs associated with monitoring of complications that occurs independent of complication onset.

Discussing financial implications of CAR-T cell therapy with patients and caregivers is imperative, including costs for inpatient vs outpatient therapy. Reimbursement implications need to be clarified and improved, and there is variation concerning whether outpatient treatment will be beneficial to both patients and institutions. In any case, we believe that inpatient versus outpatient treatment determinations should not be mandated by payers, but by patients, support systems and medical terms. However, financial solvency may be best ensured by recognizing the constantly evolving rules of reimbursement. Ideally, physicians should be able to exercise flexibility in selecting patients suitable for outpatient or inpatient therapy with no need to consider the financial burden to the patient or cost recovery to the institution in the equation. This latter model may best be in place in countries with single-payer systems, in which decisions for reimbursement are made by value framework analyses, balancing the cost of an intervention against the burden of disease, sometimes over a lifetime, rather than incident of care reimbursement models used in the USA. Disease, patient and institutional considerations for outpatient infusion of CAR-T cell therapy are summarized in table 1.[2 3 10 39 42 44–47]

CONCLUSION

Outpatient administration of CAR-T cell therapy can be feasible and safe when institutions implement policies and procedures necessary for management of this patient population. Additional findings from real-world experience with CAR-T cell therapy administered in the outpatient setting will improve outpatient policies and procedures, particularly regarding defining needs and quantifying subsequent hospital readmission following infusion. For example, time from onset of symptoms to hospital and/or ICU admission would be beneficial. Identification of reliable predictors, including biomarkers, of severe treatment-associated complications, both general and unique, as well as additional data from outpatient CAR-T cell therapy in the real-world setting, will aid in patient identification, risk reduction, and expanded outpatient administration. Recommendations concerning the potential cost savings with outpatient versus inpatient administration of CAR-T cell therapy should be based on real-world data. Given the likely expansion of CAR-T cell therapy technology and the desire to provide patients with access to transformative therapies, reimbursement guidelines should continuously be assessed.

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Competing interests GDM serves as a consultant on the study steering committee for Kymriah (tisagenlecleucel) and on the Speaker's Bureau for Kymriah (tisagenlecleucel). MRV reports salary and stock consultancy for Fate Therapeutics and reports salary from and serves on an advisory board for Novartis. AG has received consulting fees and his institution has received research funding from Acerta, Celgene, Constellation, Infinity, Infinity Verastem, Janssen, Karyopharm, Kite Pharma, Pharmacyclics, Genentech-Hoffman La Roche, AstraZeneca, Genentech and Hoffman La Roche. He is a consultant for Acerta, Celgene, Janssen, Kite Pharma, Pharmacyclics, Gilead, Medscape, MJH Associates, Physicians Education Resource and Xcenda. He has served on advisory boards for Janssen, Kite Pharma, Elsevier's PracticeUpdate Oncology, and Gilead; has served as a moderator for OncLive Peer Exchange; and has served as an Advisor on Video for AstraZeneca. He is a member of steering committees for AstraZeneca and MorphoSys and Incyte. RTM is a member and chair of the Scientific Steering Committee for Tisagenlecleucel for DLBCL and receives honoraria and research funding from Novartis. He is a consultant for and receives honoraria from CRISPR Therapeutics, Incyte, and Juno Therapeutics; receives honoraria from Kite Therapeutics; and has patents and receives royalties from Athersys. RTM is employed by Oregon Health & Science University (OHSU) and has provided consultant services to and received payment from Novartis. This potential conflict of interest has been reviewed and managed by OHSU.

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