Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee

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Chimeric antigen receptor (CAR) T-cell therapy has shown promise in patients with late-line refractory multiple myeloma, with response rates ranging from 73 to 98%. To date, three products have been approved: Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), which are approved by the US Food and Drug Administration, the European Medicines Agency, Health Canada (ide-cel only), and Brazil ANVISA (cilta-cel only); and equecabtagene autoleucel (eque-cel), which was approved by the Chinese National Medical Products Administration. CAR T-cell therapy is different from previous anti-myeloma therapeutics with unique toxic effects that require distinct mitigation strategies. Thus, a panel of experts from the International Myeloma Working Group was assembled to provide guidance for clinical use of CAR T-cell therapy in myeloma. This consensus opinion is from experts in the field of haematopoietic cell transplantation, cell therapy, and multiple myeloma therapeutics.

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Introduction

Approximately 176 404 new cases of multiple myeloma and 117 077 myeloma-related fatalities globally were estimated in 2020.[1,2] Over the past decade, advances in the treatment of multiple myeloma, including the use of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, has more than doubled the survival of patients with multiple myeloma.[3] Despite many new approved drugs and numerous combinations of these agents, resistance uniformly arises and most patients will die from their disease.[4,5] In fact, in a retrospective review, patients whose diseases were refractory to a CD38 antibody, two proteasome inhibitors, and two immunomodulatory drugs (known as penta-refractory disease) had a median overall survival of only 12·3 months.[6,7] Thus, there remains an unmet need for novel treatments for patients with highly refractory disease.

Summary of regulatory approved CAR T-cell immunotherapies

Novel immunotherapies have generated considerable enthusiasm, propelled by the identification of multiple unique targets, such as B-cell maturation antigen (BCMA), showing lineage-specific and uniform expression on malignant plasma cells.[8] The three BCMA-targeted chimeric antigen receptor (CAR) T cells (ide-cel, cilta-cel, and eque-cel) are all approved in the relapsed or refractory setting and use 4-1BB and CD3z signalling, but differ in their binding domains: murine scFv, VHH dual binding, and a fully human scFv binding domain, respectively. These BCMA-targeted CAR T cells have shown high objective response rates and extended median overall survival (appendix p 2).[9–14] This impressive anti-myeloma activity has generated considerable enthusiasm for expanding the use of CAR T-cell therapies in earlier lines of treatment. Two large, randomised trials, KarMMa-3 and CARTITUDE 4, prospectively compared CAR T-cell therapy with standard triplet therapy in patients with early relapsed or refractory multiple myeloma and both studies showed improved overall response rate and progression-free survival for patients receiving CAR T-cell therapy.[15,16] However, deaths from all-cause adverse events was higher in the CAR T group (14% *vs* 6%) in the KarMMa-3 study, suggesting that optimised management of these unique toxic effects is paramount to widespread implementation of CAR T-cell therapy in patients with relapsed or refractory multiple myeloma. This consensus aims to harmonise management providing broad recommendations on patient selection, bridging therapy, lymphodepletion, response assessments, and general toxicity management.

This consensus statement is geared towards providers at CAR T-cell treatment centres and primary haematologists and oncologists who will select patients to be referred to these centres and provide long-term care for these patients. The guideline will be updated as more products are approved and as we gain more experience of using CAR T cells for relapsed and refractory multiple myeloma.

Data collection

The consensus group panel consisted of international multiple myeloma experts from the International

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Myeloma Working Group (IMWG) Immunotherapy Committee who have experience of using CAR T-cell therapy. The panel met regularly during IMWG meetings and quarterly for IMWG Immunotherapy Sub-committee meetings since 2020. This group had regular discussions on emerging data for CAR T-cell therapy. Members also reviewed key publications, professional society recommendations, and conference presentations involving CAR T-cell therapy in relapsed or refractory multiple myeloma up until June 30, 2023. The group did not receive any external funding support for the work.

Guidelines

Patient selection

US Food and Drug Administration (FDA) approval for cilta-cel and ide-cel is for patients who have received at least four previous lines of therapy, while European Medicines Agency approval is for patients with at least three previous lines. Response rate and progression-free survival were comparable for patients treated with three versus four or more previous lines of therapy,[17,18] which could be due to drug class refractoriness being more prognostic than number of lines of therapy. Ideally, patients should be evaluated at the CAR T-cell therapy centre during their third line of therapy in the USA and second line of therapy in Europe. It is important to use IMWG criteria for counting previous lines of therapy when considering CAR T-cell treatment referral and use of other immunotherapies,[19] which includes new lines of therapy started for refractory disease, relapsed disease, or intolerance to therapy due to toxicity.

Several disease and treatment-related features might jeopardise the patient's eligibility for CAR T-cell therapy, including bulky or rapidly progressive disease which increases the risk of clinical deterioration during washout for leukapheresis or CAR T-cell manufacturing, ongoing severe cytopenia that limits the ability to safely undergo apheresis and successfully produce CAR T cells, and exposure to high doses of alkylator that can negatively affect peripheral blood lymphocyte counts and T-cell fitness for CAR T-cell manufacturing.[20–22] Although patients with high-risk features, including the presence of adverse cytogenetics, extramedullary disease, and advanced stage tend to have poorer clinical response to all conventional therapies, these patients can still benefit from CAR T cells and should not be excluded from treatment.[22,23] Patients with active plasma cell leukaemia, secondary CNS involvement, poor renal function (creatinine clearance <30 mL per min), and secondary amyloidosis were excluded from both KarMMa-1 and CARTITUDE-1 studies, therefore the safety of BCMA CAR T-cell therapies in these situations remains to be defined. Successful results from case reports are available, but ongoing trials in these patients will help guide future use.[24–27] Additional considerations for CAR T-cell therapy eligibility from the IMWG panel are reported in the survey results (appendix pp 6–9). Panel 1 summarises recommendations for patient selection, including considerations for previous therapies, disease characteristics, and organ functions.

Previous therapies

Whenever possible, the patient's referring haematologist and CAR T-cell therapy physician should discuss the choice and timing of salvage treatment before leukapheresis as there are a number of drugs that can negatively affect peripheral blood lymphocyte counts and T-cell fitness before apheresis and CAR T-cell manufacturing. In particular, lymphotoxic drugs, such as bendamustine, cyclophosphamide, melphalan, fludarabine, and high-dose steroids, might have extended effects in the range of many months and should be avoided at least in the immediate 1–2 months before leukapheresis and possibly longer.[20,22,23,28,29] For common anti-multiple myeloma drugs, a 2-week washout period is standard to allow for blood count recovery. For drugs with short half-lives, such as low-dose corticosteroids, immunomodulatory drugs, and venetoclax, withholding them for five half-lives might be reasonable, even if for less than 14 days. Restricted radiation to a symptomatic plasmacytoma, without washout, is reasonable when the radiation field involves less than 5% of the bone marrow volume. Although many CAR T-cell therapy studies have excluded previous allogeneic stem-cell transplantation, the CARTITUDE-1 study successfully enrolled seven patients with previous allogeneic stem-cell transplantation with no unexpected toxicity or graft-versus-host disease.[30]

Although the CAR T-cell manufacturing success rate was high in all three registration studies, the FDA approved product release specification is narrower than that used in clinical trials, and manufacturing failure has been problematic in the real world. Given the potential need for repeat leukapheresis should the first manufacturing fail, lymphotoxic drugs should ideally be avoided for bridging therapy if suitable alternatives exist. Panel 1 summarises recommendations for consideration of myeloma treatment before leukapheresis.

Previous BCMA-targeted therapy

For both KarMMA-1 and CARTITUDE-1 studies, and others in earlier lines of therapy (KarMMa-3 and CARTITUDE-4), BCMA expression on plasma cells was not required for enrolment. There was no difference in clinical response based on immunohistochemistry expression of BCMA in the bone marrow.[9,10] Other BCMA-targeted therapies are now available; their use might affect BCMA expression on myeloma cells at the time of relapse and the likelihood of response for subsequent BCMA-targeted therapy.[31,32] Ongoing clinical trials that are enrolling patients with previous BCMA-targeted therapies will help inform the effect of previous exposure to BCMA-targeted therapy on CAR T-cell therapy clinical outcomes (appendix p 4).

Panel 1: Summary recommendations for patient selection and management during treatment

Recommendations for patient selection

- Patients should be referred early for consideration of chimeric antigen receptor (CAR) T-cell therapy evaluation given the limited access to manufacturing slots. Early referral can help facilitate discussion of salvage therapy considerations to optimise segueing to leukapheresis.
- Patients who are eligible for both CAR T-cell therapy and T-cell engagers should be considered first for CAR T-cell therapy.
- There is no absolute age limit for consideration of CAR T-cell therapy; however, frailty and individual physiologic fitness should be considered.
- Although experience remains limited with patients on dialysis, growing experience in patients with renal dysfunction suggest feasibility for CAR T-cell therapy using renal dose adjusted fludarabine.
- When possible, avoid lymphotoxic drugs as part of the salvage therapy immediately before leukapheresis.
- Previous exposure to other B-cell maturation antigen (BCMA)-targeted therapy could negatively affect clinical response to CAR T cells. Loss of BCMA expression could become more prevalent due to treatment selection pressure with increased availability of BCMA-targeted therapies. Due to the absence of a clinically available test for BCMA loss, consideration should be given whenever available for therapy targeting a different antigen at first relapse.

Recommendations for myeloma treatment before CAR T-cell therapy

- Before leukapheresis:
  - Consider drug half-life, drug effect on number and fitness of T cells, and clinically feasible washout period to optimise the collected T cells for CAR T-cell manufacturing.
  - Avoid lymphotoxic drugs, such as bendamustine and high-dose cyclophosphamide, where possible.
  - A washout period of 14 days for chemotherapy drugs should be used when possible to allow for T-cell count recovery.
  - For radiation that involve less than 5% of the bone marrow, a washout period might not be needed.
  - For corticosteroids and immunomodulatory drugs with a short half-life, the washout period can be reduced to 7 days.
- After leukapheresis (bridging therapy):
  - Disease burden and previous kinetics of disease progression should be considered to guide the selection of bridging therapy.
  - Given the increased risk for more severe cytokine release syndrome and immune effector cell associated neurologic syndrome (ICANS), immune effector cell associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), and late neurologic symptoms in patients with high disease burden or rapidly progressing disease, priority
  - should be placed on a regimen involving agents to which a patient's disease has not become refractory.
  - For patients with low disease burden that is not rapidly progressing, consider the minimum therapy needed to limit disease progression during CAR T-cell manufacturing to reduce risk of organ toxicities and serious side-effects that might delay or preclude CAR T-cell infusion, which could include continuing the same regimen before leukapheresis.
  - Preclinical data suggest immunomodulatory drugs and anti-CD38 antibodies might improve T-cell function and CAR T-cell activities; these drugs can be used with consideration for washout as needed to allow count recovery before lymphodepletion chemotherapy.
  - Given the unknown risk for CAR T-cell manufacturing failure in clinical practice, consider avoiding lymphotoxic drugs (eg, bendamustine or high-dose cyclophosphamide) when possible if re-collection of T cells might be required for repeat CAR T-cell manufacturing.
  - The effect of other BCMA-targeted therapy immediately before CAR T-cell therapy is unknown at this time; therefore, due to potential concern for down-regulation of antigen expression, these are not recommended if alternative therapies are available.

Recommendations for cytokine release syndrome management

- Cytokine release syndrome management should be aligned with regulatory Risk Evaluation and Mitigation System (REMS) by the US Food and Drug Administration and Risk Management Plans (RMP) from the European Medicines Agency for each CAR T-cell product. General guidelines include:
  - Supportive care with antipyretics and fluid resuscitation as primary intervention.
  - Use of tocilizumab with or without dexamethasone for persistent grade 1 cytokine release syndrome, or for early or rapid onset cytokine release syndrome.
  - There is low threshold to use tocilizumab in grade 1 cytokine release syndrome, such as in patients who are frail, those with high disease burden, or high levels of inflammatory markers (eg, ferritin or C-reactive protein) at the time of CAR T-cell infusion.
  - Steroids should be added in grade 3 and higher cytokine release syndrome and when cytokine release syndrome persists despite two doses of tocilizumab.
  - Consider adding alternative immunosuppressive agents once two or more doses of tocilizumab have been given.
- Consider tocilizumab with or without dexamethasone for the following regardless of cytokine release syndrome grading, in addition to grading-based management:
  - Atrial fibrillation with rapid ventricular response.
  - Decrease in cardiac ejection fraction by Common Terminology Criteria for Adverse Events (CTCAE) criteria.
  - Grade 3 or higher transaminitis (CTCAE criteria) not attributable to other causes.

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See **Online** for appendix

(Panel 1 continued from previous page)

- Grade 3 or higher renal dysfunction (CTCAE criteria) not attributable to other causes.
- Concurrent evaluation for infections is essential.
- Consider tocilizumab, dexamethasone, and anakinra for early signs of IEC-HS, macrophage activation syndrome-like, or persistent immune activation.

Recommendations for ICANS management

- Evaluation and assessments:
  - Baseline brain imaging and comprehensive neurologic assessment by a neurologist before CAR T-cell infusion ensures accuracy in assessing new neurologic deficits post-CAR T-cell infusion.
  - Handwriting should be part of ICANS assessment as handwriting changes can identify early onset of ICANS, and micrographia is an early change seen with the onset of Parkinsonism.
  - Work closely with neurology or neuro-intensive care units for neurological monitoring during ICANS.
  - Consider electroencephalogram, brain MRI, and intracranial pressure monitoring with the onset of altered levels of consciousness, focal motor weakness, or paresis.
  - Prophylactic anti-seizure medications can be used in the first month after CAR T-cell infusion for patients at high risk for ICANS.
- ICANS in the acute management setting (first month post CAR T-cell infusion):
  - ICANS most commonly occurs during or after cytokine release syndrome in the first 1–2 weeks post-infusion and is generally completely reversible; management should be aligned with REMS and RMP for product-specific ICANS management.
  - For ICANS with deficits measurable on immune effector cell encephalopathy (ICE) score that are improving on treatment:
    - De-escalate steroid as rapidly as tolerated as long as ICE score does not worsen.
    - For patients with persistent grade 1 ICANS for weeks to months with no effect on activities of daily living or safety, corticosteroids can be discontinued.
  - Rapid escalation of therapy should be considered for patients with grade 3 or 4 ICANS (anakinra can be useful),[12] especially due to seizure and cerebral oedema that is not improving with corticosteroids.
  - If occurring during CAR T-cell expansion or with evidence for rapid lymphocyte expansion, consider lymphotoxic drugs, such as high-dose cyclophosphamide or antithymocyte globulin.
- ICANS in the subacute to late onset setting:
  - Guillain–Barré syndrome, cranial nerve palsies, and Parkinsonism have been reported.
  - REMS and RMP should continue to be followed for abstaining from operating motor vehicles for 8 weeks after CAR T-cell infusion.
  - Patients, caregivers, and the home clinical team should be informed to monitor for handwriting changes and new neurologic symptoms related to the above syndromes.
  - Contact CAR T-cell treatment centre and assessment with neurologist for new neurologic symptoms.

Both genomic deletion and loss of functional recognition and binding are reported for BCMA post CAR T-cell therapy.[33,34] There is a need to develop clinically available tests to detect genomic and functional loss of BCMA to help guide subsequent therapy selection. In the absence of a clinically available assay to detect BCMA loss, given that BCMA expression can commonly be observed at the time of progression and increase over time, patients might benefit from receiving an alternative non-BCMA-directed therapy before proceeding with another BCMA-directed therapy.

T-cell exhaustion is reported in patients who are refractory to or relapsed after BCMA T-cell engagers (TCEs). A treatment-free period from bispecific antibodies might help improve T-cell fitness.[35] Whether the use of immunomodulatory drugs, cereblon E3 ligase modulatory drugs, or anti-CD38 monoclonal antibody after TCE treatment could improve T-cell function remains to be explored. Emerging clinical trial data and real-world experience will help inform whether and how BCMA CAR T-cell therapy should be considered in this setting.[32] We recommend for patients who could qualify for both TCE and CAR T-cell therapies to be considered for CAR T-cell therapy first.

Repeat CAR T-cell dosing

Repeat dosing of the same CAR T-cell treatment has not yielded durable clinical responses in ide-cel or cilta-cel trials.[9,23] The potential benefit of administering additional doses of the same CAR T-cell therapy while a response is ongoing has yet to be determined and some preliminary results suggest a potential improvement in response.[36] We do not recommend repeat treatment with the same CAR T-cell therapy at the time of relapse. However, CAR T-cell treatment targeting a different antigen or binding domain could still be considered.

Organ function and comorbidities

Age should not restrict eligibility for CAR T-cell therapy.[9,10,37] Cardiopulmonary fitness and frailty might be more relevant as eligibility criteria, as a patient needs to be able to tolerate CAR T-cell therapy-associated side-effects. Recommended organ function testing is listed in panel 2.

Renal dysfunction is a common complication of myeloma. Given previous studies on the importance of fludarabine lymphodepletion for CAR T-cell activities, renal clearance above 45 mL per min is required in

clinical trials to allow fludarabine dose reduction, but not omission. Patients requiring haemodialysis were excluded from these trials. The US Myeloma Immunotherapy Consortium showed that among 196 patients undergoing leukapheresis for ide-cel manufacturing in standard of care practice, 75% would not have been eligible for the KarMMA trial, with the most common reason being organ dysfunction (28%) followed by renal dysfunction (13%).[38,39,40] Similarly, the consortium reported that among the 143 patients undergoing leukapheresis for cilta-cel manufacturing in standard of care practice, 57% would not have been eligible for the CARTITUDE-1 trial, with 12% due to organ dysfunction.[41] Early follow-up of the patients from both of these real-world analyses showed comparable safety and clinical responses compared with KarMMa despite the-real world patients being less fit. However, a CIBMTR (Center for International Blood and Marrow Transplant Research) analysis of 821 patients receiving standard-of-care ide-cel showed a significantly reduced progression-free survival and overall survival in patients who received bendamustine.[39] There are additional case reports of the safe use of cyclophosphamide alone or with dose-adjusted fludarabine in patients with end-stage renal disease.[39,40]

Infection screening

CAR T-cell therapy should not be administered in patients who might have active infections, including chronic viral infections; hepatitis and HIV; and reactivation of cytomegalovirus, Epstein–Barr virus, and parvovirus B19, among others. Before initiating CAR T-cell therapy, patients should be evaluated for: HIV antibodies; hepatitis B virus surface antigen, surface antibody, and core antibody; and hepatitis C virus antibody with reflex nucleic acid testing if any of the tests suggest active or chronic hepatitis. For patients in endemic regions or with previous exposure or infections, screening for cytomegalovirus, parvovirus B19, or other past infections, including invasive fungal infections, mycobacterial, or atypical mycobacterial infections, might be appropriate. Of note, case reports describing successful CAR T-cell treatment in patients with active HIV infection are emerging.[42] Asymptomatic viral electrocardiogram of upper respiratory viruses, such as SARS-CoV-2, should not preclude initiation of potentially life-saving CAR T-cell therapy.[43,44] Cytomegalovirus viremia without clinical evidence for infection should be treated before leukapheresis or CAR T-cell therapy. Epstein–Barr virus viremia without clinical evidence for infection could be treated, but would not be a contraindication to leukapheresis or CAR T-cell therapy.

Referral logistics

Manufacturing access to approved CAR T-cell treatments has been restricted. Many certified treatment centres in the USA receive few manufacturing slots per month and have long waiting lists.[45] Early referral, particularly for patients with aggressive disease, can help decrease the waiting time. Providing updated clinical information, particularly noting the time of progression and change of therapy, can be helpful for the CAR T-cell therapy team for maintaining the waiting list and selecting patients, and providing guidance on salvage therapy before leukapheresis. In addition, given the disparities in patient access to care, treatment centres should consciously strengthen community engagement in their catchment area to improve access for ethnic minorities and patients who are socioeconomically disadvantaged.[46,47]

Panel 2: Baseline testing and timing of pre-CAR T-cell therapy assessments

These organ function tests should be performed at the time of initial CAR T-cell therapy evaluation and can be repeated before lymphodepletion chemotherapy if there is concern about clinical changes involving these organs.

- Cardiac:
  - Electrocardiogram with 12 leads
  - Echocardiogram or multi-gated acquisition scan
- Respiratory:
  - Pulse oximetry on room air (for patients with pO_2 <92% on room air or pre-existing pulmonary disease, pulmonary function tests can be performed)
- Renal:
  - Creatinine (consider cystatin C or iothalamate clearance if renal insufficiency is present to guide renal dosing of fludarabine)

Therapy during CAR T-cell manufacturing

More than two-thirds of the patients in the KarMMa-1 and CARTITUDE-1 studies received bridging therapy, defined as anti-myeloma therapy given after leukapheresis and before lymphodepletion chemotherapy. Disease control and avoidance of organ dysfunction while awaiting manufacturing was the priority. Although patients were required to receive previous exposed regimen only during the CAR T-cell manufacturing period on the registration studies, subsequent ongoing CARTITUDE studies allowed the use of new regimens during bridging to reduce tumour burden as part of the mitigating strategies to reduce the risk of late onset neurologic auto encephalitis that included Parkinsonism.

For patients with no measurable disease after bridging therapy, the effect of the lack of antigen expressing myeloma cells on CAR T-cell persistence and efficacy remains unanswered. Active trials in front-line therapy where CAR T-cell therapy is given after induction will generate information on the CAR T-cell persistence and efficacy with minimal to no measurable disease. Although a bridging regimen is selected for its likelihood

of inducing a clinical response, CAR T-cell therapy should be given as early as it is available and when the patient is deemed clinically safe to receive the therapy. It is not necessary to delay CAR T-cell therapy until the deepest response is achieved with bridging therapy. Panel 1 summarises myeloma treatment considerations during CAR T-cell manufacturing (bridging therapy).

Out-of-specification CAR T-cell products

Out-of-specification CAR T-cell therapies have product release criteria specifications (most commonly viability and CAR+ T-cell number) that are outside of the FDA approved range, but within the range used in registration studies. These products could be given as part of an expanded access protocol or managed access protocol. Until clinical outcomes are available from these protocols, it is reasonable to consider that the likelihood of comparable clinical response from out-of-specification CAR T-cell products is high. Of note, CAR+ T-cell dose has been found to be positively correlated with increased progression-free survival with ide-cel.[9] Providers are encouraged to discuss with the manufacturer the parameters that are out of specification, the likelihood for repeat manufacturing to meet release criteria, and the likelihood that a patient can undergo repeat leukapheresis (if needed) or can wait for repeat manufacturing. In the scenario where repeat leukapheresis or further manufacturing delay is not clinically feasible, using an out-of-specification CAR T-cell product under an expanded access protocol or managed access protocol is a reasonable option.

Lymphodepletion chemotherapy

The earliest clinical trials with cilta-cel in China used cyclophosphamide only as lymphodepletion. However, both cyclophosphamide and fludarabine were used in all three registration studies. In 2022, there was a shortage of fludarabine in the USA, which raised the question of omission of fludarabine or alternative lymphodepletion regimens for CAR T-cell therapy. Recent fludarabine shortages have led to some institutions using bendamustine; however, the long-term implications of this intervention are not clear.[48–50] While additional studies on the effect of alternative lymphodepletion chemotherapies on outcomes of CAR T-cell therapy are needed, adherence to the type of lymphodepletion chemotherapy specified by the package insert for respective CAR T-cell products, with appropriate adjustment for renal dysfunction if needed, is recommended whenever feasible.

Cytokine release syndrome management

Cytokine release syndrome is a well-known toxicity following CAR T-cell treatment and the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system is the standard to assess cytokine release syndrome grades.[51] However, management of cytokine release syndrome should take into account all the potentially affected organs (panel 1).

Disease features, patient's comorbid conditions, and CAR T-cell product design all contribute to cytokine release syndrome. In myeloma CAR T-cell therapy registration studies, cytokine release syndrome has mostly been low grade and manageable (appendix p 3). While having an individual Risk Evaluation and Mitigation System (from the US FDA), each CAR T-cell product can become administratively burdensome. Study experience for cytokine release syndrome interventions, particularly considerations for the use of third-line agents, such as anakinra, will be informative to ensure a similar safety profile when the CAR T-cell therapy is used in practice. Current data support the use of tocilizumab in grade 2 cytokine release syndrome, or grade 1 cytokine release syndrome with early onset or rapid progression or persistence greater than 72 h. The use of tocilizumab and steroids does not affect treatment response.[52,53] Therefore, intervention early in cytokine release syndrome should be considered to optimise safety in patients with higher disease burden and in patients who are frail due to comorbidities. Early initiation of cytokine release syndrome treatment can help reduce the likelihood of immune effector cell associated neurologic syndrome (ICANS). There are currently no data to support the use of prophylactic cytokine blockade to manage cytokine release syndrome after CAR T-cell treatment for myeloma.

Immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome

Haemophagocytic lymphohistiocytosis and macrophage activation syndrome are rare, but highly fatal, complications post CAR T-cell treatment. These conditions can escalate with uncontrolled hyper-inflammation during cytokine release syndrome or after its resolution. The reported incidence of haemophagocytic lymphohistiocytosis and macrophage activation syndrome is approximately less than 8% across studies.[9,10] However, diagnosis for CAR T-cell-associated haemophagocytic lymphohistiocytosis and macrophage activation syndrome is challenging given the overlapping signs and symptoms with cytokine release syndrome. Recently, ASTCT published an expert opinion for uniform criteria to define immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) in an effort to better describe the incidence of this condition across different CAR T-cell therapies.[54] There is also no consensus management guideline, however, expert opinions suggest the sequence of IL-6 blockade and corticosteroids followed by additional cytokine blockade, such as anakinra, and targeted therapy, such as ruxolitinib. Emapalumab, an interferon-gamma antibody, is FDA-approved for primary haemophagocytic lymphohistiocytosis, and was recently reported to be used in this setting in paediatric IEC-HS in B-cell acute lymphoblastic leukaemia.[55] Management

of IEC-HS is challenging given the confounding complications (eg, infections and cytopenia); thus, early intervention when clinical suspicion is high before meeting full haemophagocytic lymphohistiocytosis diagnostic criteria is recommended. If the patient has already received IL-6 blockade and steroids as part of the management for cytokine release syndrome or has not improved with these interventions, drugs that can affect the myeloid pathway are recommended, including anakinra and ruxolitinib. Furthermore, if there is evidence of CAR T-cell expansion or persistence, lymphotoxic drugs such as cyclophosphamide or antithymocyte globulin should be considered.

ICANS management

Neurotoxicity is another common CAR T-cell treatment-associated side-effect, but the mechanism of action is less well understood than the mechanism of cytokine release syndrome. Associations have been made between the breakdown of the blood brain barrier and endothelial activation.[56] BCMA expression has been reported in the CNS in one case report.[57] The most common occurrence of neurotoxicity is during cytokine release syndrome. Early signs and symptoms include decreased concentration and word-finding difficulty, which can progress to dysphasia, aphasia, confusion, and agraphia. Seizures and cerebral oedema have also been reported as rare occurrences. The ASTCT consensus grading guideline for ICANS is the current standard.[51] Management recommendations are summarised in panel 1.[58]

While studies of myeloma CAR T-cell therapy vary in the types of neurologic symptoms reported (including using different grading systems), ICANS specific presentations are usually low grade and reversible (appendix p 3). The overall report of cerebral oedema is low. Of note, delayed atypical neurologic deficits after the resolution of cytokine release syndrome were reported for cilta-cel in the CARTITUDE-1 study.[59] Cranial nerve palsies, Parkinsonism, and Guillain–Barré syndrome have also been reported (appendix p 3). Another study using the same CAR construct (LCAR-B38M, Legend, Biotech, Nanjing, China), conducted in China did not report similar neurologic findings.[60] Follow-up of a larger population across ongoing CARTITUDE studies is needed to understand the incidence and clinical course of the delayed neurotoxicity, but risk factors appear to include high-grade cytokine release syndrome, previous ICANS, high tumour burden, and rapid expansion of CAR T cells. Subsequent CARTITUDE studies have used mitigation strategies, including early and aggressive treatment of cytokine release syndrome and enhanced cytoreduction, to reduce tumour burden, which so far appears to have decreased the rate of Parkinsonism considerably from 6% to 1%, but facial nerve palsy was still seen in one patient in CARTITUDE-2 and in 16 (9·1%) in CARTITUDE-4.[16,32]

Although IL-6 blockade can be used to temper cytokine release syndrome during ICANS, dexamethasone is most commonly used initially for its CNS penetration with low side-effect profiles. There might be an increase in risk of ICANS with IL-6 receptor blockade with tocilizumab, possibly due to an increase in circulating serum IL-6.[61,62] ICANS has also been observed to resolve without dexamethasone. Vigilant monitoring and testing for seizures and cerebral oedema are important. Identification of seizures would warrant escalation of steroids and use of anti-epileptic medications. Similarly, given the risk for rapid deterioration and high mortality, cerebral oedema should escalate the need for closer intensive care unit monitoring for intracranial pressure and escalation of treatment. High-dose methylprednisolone is frequently used. IL-1 pathway blockade with anakinra has also been commonly used, while lymphotoxic medications, such as cyclophosphamide and antithymocyte globulin, can be used for refractory cases.[63]

Haematological toxicity management

Although cytokine release syndrome and neurotoxicity have received the most attention, haematological toxicity occurs universally with CAR T-cell treatment and aggressive supportive care is required. The aetiology is multifactorial, including previous myeloma therapy, pre-existing clonal haematopoiesis, lymphodepletion chemotherapy, cytokine release syndrome and medications used for its management, and infections.[64,65] Severe neutropenia, anaemia, thrombocytopenia, and leukopenia generally occur in more than 50% of CAR T-cell treatment recipients (appendix p 5) and are now referred to as immune effector cell-associated haematotoxicity.[9,10,66–68] Delayed recovery is common, with resolution to normal blood counts often taking 6–12 months.[9,10,66–68] Thus, close monitoring of haematological recovery with continued supportive care, including growth factor and transfusion therapy, is required for the first 6–12 months after CAR T-cell therapy. Risk factors for immune effector cell-associated haematotoxicity can be identified before lymphodepletion chemotherapy with the CAR-HEMATOTOX score,[67] which is being studied to guide management in the future on the basis of risk.[68]

Recommendations for cytopenias and supportive care

Since cytopenias are universal for patients receiving CAR T-cell treatment, close blood count monitoring and blood product support at the onset of severe anaemia and thrombocytopenia should be provided per institutional guidelines. In most trials, growth factor support has been avoided during the risk period for cytokine release syndrome or during active cytokine release syndrome or ICANS, with the hypothetical concern that their use might worsen acute toxicity or inflammation, or potentially promote macrophage activation syndrome-

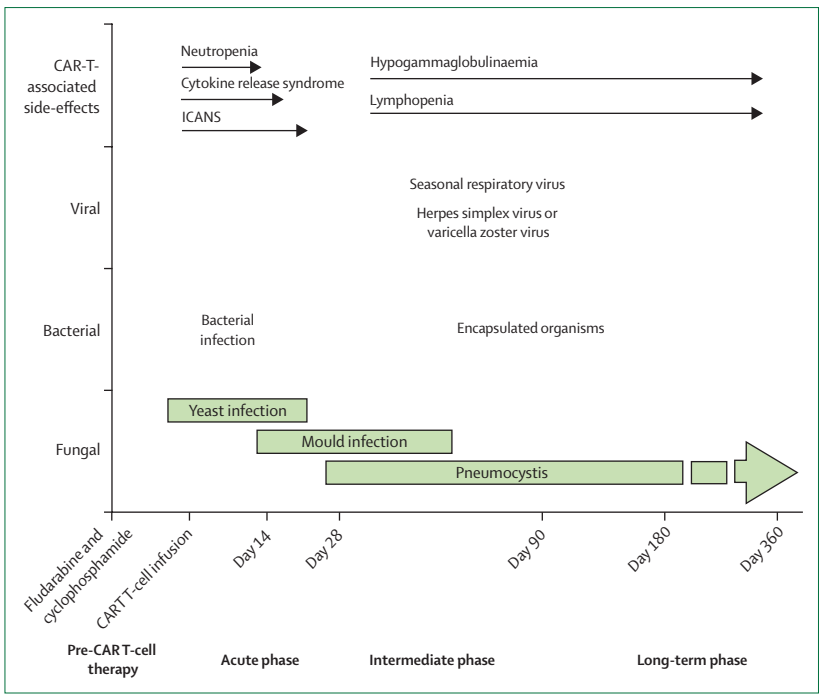

Figure: **Timeline of immune suppression and infection risks after CAR T-cell therapy**
ICANS=immune effector cell associated neurologic syndrome.

Panel 3: High-risk features for opportunistic infection

- Prolonged neutropenia longer than 3 weeks
- Use of dexamethasone 10 mg daily for more than 3 days or methylprednisolone 1 g per day
- Use of more than one dose of tocilizumab or evidence of severe (grade 3 or 4) cytokine release syndrome
- Use of second-line agents for management of cytokine release syndrome, haemophagocytic lymphohistiocytosis, or immune effector cell-associated neurologic syndrome (ie, anakinra, siltuximab, etoposide, or cyclophosphamide)

like symptoms. There is some data that suggest it might be safe to use granulocyte colony stimulating factor early in the treatment course without untoward effects.[69] The use of growth factors should be considered after the cytokine release syndrome risk period (commonly after day 14), and in patients experiencing delayed or late cytopenias. Similarly, erythropoietic and thrombopoiesis-stimulating agents could be considered for long-lasting and severe anaemia or thrombocytopenia per institutional guidelines.

Autologous stem-cell boost, without conditioning chemotherapy, appears to have the most consistent success to improve blood count recovery in patients who have long-term and severe cytopenias.[70,71] A median dose of $2{\cdot}75\times10^6$ CD34+ stem cells per kg administered without conditioning chemotherapy was given to 19 patients at a median of 53 days after CAR T-cell infusion, with 95% success for engraftment. As a precaution, collection and storage of autologous stem cells after leukapheresis for CAR T-cell manufacturing should be considered in patients receiving CAR T-cell therapy in earlier lines and in those who do not already have stem cells stored.

Infections

Infections are common in patients undergoing CAR T-cell therapy.[72–75] The types of infection and pathogens vary according to four different phases of the CAR T-cell therapy continuum (figure).[75] Pneumocystis pneumonia has been described, predominantly occurring in patients where prophylaxis was discontinued at an early timepoint (90 days) after CAR T-cell treatment. Clinically significant viral reactivation, including cytomegalovirus, Epstein–Barr virus, and parvovirus B-19, have been described, but the incidence remains low and few cases of cytomegalovirus viremia with end-organ disease have been reported.[76] Features contributing to a higher risk for infections are summarised in panel 3. Late infections are rare but occur in the setting of profound and long-term lymphopenia and hypogammaglobulinemia.

Acute infections

Fever with cytokine release syndrome frequently occurs together with neutropenia. Patients require close monitoring and aggressive therapy for possible infection. Management of neutropenic fever per institutional guidelines should be continued. Medications to manage cytokine release syndrome and ICANS can mask fever, and vigilant infection monitoring should be continued. Empirical use of antivirals or mould-active antifungal therapy should be considered. Screening for viral reactivation (cytomegalovirus, parvovirus, and Epstein–Barr virus) and opportunistic infections (pneumocystis jirovecii pneumonia and varicella zoster virus) can be considered in patients at the highest risk for these opportunistic infections and treatment of viral reactivation should be guided by institutional algorithms. The use of growth factors and replacement gamma globulin should also be considered.

Antimicrobial prophylaxis

Antimicrobial prophylaxis has been the mainstay for infection prevention in immunocompromised hosts. Table 1 summarises current European Society for Blood and Marrow Transplantation and the new IMWG recommendations for prophylaxis against the most common infections in patients with relapsed or refractory multiple myeloma receiving BCMA-directed CAR T-cell therapy. These recommendations have been developed based on current data and regional practices, and are supported by a 2020 paper which focused on antimicrobial prophylaxis in patients receiving CD19-targeted CAR T-cell therapy.[76] Since the incidence and types of infection might vary by region and by the CAR T-cell product

administered, institutional practices should be used to augment these guidelines as appropriate.

Immunoglobulin replacement

The use of replacement immunoglobulins (intravenous or subcutaneous immunoglobulin) is controversial, given the absence of clinical trial data, but can be considered in patients with severe hypogammaglobulinemia (IgG levels <400 mg per dL) or in those with moderate hypogammaglobulinemia (IgG levels 400–600 mg per dL) and recurrent or severe infections. In patients with IgG myeloma, the Hevylite test (Binding Site, Thermo Fisher Scientific, CA, USA) or total IgG level minus monoclonal protein (M-protein) can be used to estimate the non-myeloma IgG level for intravenous immunoglobulin replacement consideration. Therapy can begin before CAR T-cell therapy and continue for at least the first 3–6 months after CAR T-cell treatment, with the goal of maintaining the IgG level more than 400 mg per dL. Institutional guidelines for replacement intravenous immunoglobulin should be followed in patients with recurrent infections.

Vaccinations

There is a paucity of data to guide vaccination strategies in patients with multiple myeloma receiving CAR T-cell therapy. The long-term effects of BCMA-targeted CAR T-cell therapy on humoral immunity are not well studied. However, hypogammaglobulinemia is commonly seen following BCMA-directed CAR-T therapy and can last for 6–12 months or longer (appendix p 5). There are also patients who have few or no plasma cells detected in bone marrow samples obtained at 1 year following CAR T-cell therapy. Thus, further studies are needed before formal vaccination guidelines for patients undergoing CAR T-cell therapy can be made. Some centres have begun to vaccinate CAR T-cell treatment recipients following guidelines developed for stem-cell transplantation recipients. It would be prudent to avoid live vaccines until further data are available. Vaccines, particularly those for high-risk respiratory infections, such as influenza and respiratory syncytial virus, could be given before and after CAR T-cell therapy as per institutional guidelines.

Regarding COVID-19 vaccines, some patients undergoing CAR T-cell treatment have received RNA-based vaccinations, but the efficacy of these vaccines has not been rigorously studied. Many centres are currently monitoring for the presence of anti-COVID-19 spike protein antibodies and cell-mediated responses. Of note, there are no reports of suspected harm following COVID-19 vaccination and centres have recommended administering COVID-19 vaccinations as early as 1 month after CAR T-cell therapy. The optimal timing and the clinical effectiveness of the different COVID-19 vaccines in patients receiving CAR T-cell therapy are unknown.

Response assessment

Herein, the IMWG propose a uniform approach to response assessments in patients receiving CAR T-cell therapies for multiple myeloma. Updated and specific criteria are necessary due to the unique logistics of this novel therapy and to harmonise response assessments for all patients receiving CAR T-cell therapy across the multiple myeloma treatment continuum.

	EBMT[75] recommendation	IMWG recommendation	Comments
Antiviral prophylaxis	Valacyclovir 500 mg twice a day and acyclovir 800 mg twice a day from lymphodepletion for 1 year post-CAR T-cell therapy	Valacyclovir 500 mg twice a day and acyclovir 400–800 mg twice a day from lymphodepletion for 1 year post-CAR T-cell therapy	Late varicella zoster virus has been described
Antibacterial prophylaxis	Not recommended	Levofloxacin 500 mg daily (or equivalent)	To start at neutropenia (ANC <500 per uL) or during high steroid or multiple immunosuppressive medication use
Antifungal prophylaxis	Not recommended	Fluconazole 400 mg daily (or equivalent); prophylaxis against mould (eg, aspergillus) should be considered in high-risk situations	To start at neutropenia (ANC <500 per uL) or during high steroid or multiple immunosuppressive medication use
Anti-pneumocystis prophylaxis	Co-trimoxazole 480 mg daily or 960 mg three times a week pre-lymphodepletion for 1 year post-CAR T-cell therapy	Sulfamethoxazole 800 mg and trimethoprim 160 mg three times a week pre-lymphodepletion until 6 months post-CAR T-cell therapy; alternatives could be considered in settings of cytopenia, allergy, or regional drug access; alternatives include monthly pentamidine nebuliser or atovaquone (1·5 g daily)	Late infections occur and continue therapy until CD4+ count >200 cells per uL
Intravenous gamma globulin	Consider in adults who have had encapsulated organism infections	Consider IgG replacement if IgG <400 mg/dL with 400–500 mg/kg intravenous immunoglobulin every 4–6 weeks	No formal studies, consider replacement if recurrent infections and IgG is 400–600 mg/dL*
G-CSF use	Consider G-CSF to shorten duration of neutropenia from 14 days after CAR T-cell infusion	Should be used to maintain ANC >1000 per uL in the first 3 months after CAR T-cell infusion	Avoid during cytokine release syndrome or ICANS, or if presenting with macrophage activation syndrome-like symptoms

ANC=absolute neutrophil count. EBMT=European Society for Blood and Marrow Transplantation. G-CSF=granulocyte-colony stimulating factor. ICANS=immune effector cell-associated neurotoxicity syndrome. IMWG=International Myeloma Working Group. *Correct IgG level for IgG paraprotein—eg, if a residual M-spike of 0·4 g/dL IgG-kappa exists and the total IgG level is 700 mg/dL, then the correct IgG would be estimated around 300 mg/dL.

Table 1: **Antimicrobial prophylaxis**

Recommended assessments

CAR T-cell therapy parallels autologous stem-cell transplant therapy in terms of logistics. Thus, some principles of response assessments in stem cell transplantation can also be used for CAR T-cell therapies.

The standard of care is that physicians will not be restricted to previously used regimen only and can use a new regimen and have a higher likelihood of anti-myeloma activities for bridging and some patients might have complete response before initiation of lymphodepletion chemotherapy, which could become more common as CAR T-cell therapy is used as part of front-line consolidation therapy. To date, in clinical trials, patients achieving a complete response before CAR T-cell infusion have been considered not evaluable for response; we propose including these patients in the response evaluation. Baseline assessments should occur at the time when the disease is measurable—ie, at diagnosis when CAR T cells are used as part of front-line therapy, and at relapse before leukapheresis and initiation of planned bridging therapy.

The proposed schedule for baseline assessments is shown in table 2. Response assessments should be performed throughout the treatment continuum using the baseline values to quantify response. The recommended post-CAR T-cell treatment assessments are shown in table 3, which includes the minimum accepted frequency of testing; the treating facility might perform assessments more frequently. In general, assessment of blood and urine M-protein, including serum protein electrophoresis tests, serum immunofixation tests, serum free light-chain assays, urine protein electrophoresis tests, and urine immunofixation electrophoresis, should be performed at days 30, 90, 180, 270, and 360 and at least every 3 months thereafter. Bone marrow biopsy and aspirates are recommended after CAR T-cell therapy at day 30 or 90, 180, 360, and at any timepoint to confirm complete response as clinically indicated, and annually thereafter for serial minimal residual disease (MRD) monitoring. MRD testing can be assessed in patients achieving very good partial response or better, at the time of bone marrow sampling. Radiology assessments, including PET–CT, MRI, or weight-bearing CT scan, might be required to assess response for patients with evidence of soft-tissue extramedullary disease. Patients with soft-tissue extramedullary disease should have radiology assessment of disease performed at baseline and at minimum on approximately days 90, 180, 270, and 360 and to confirm complete response or progressive disease as clinically indicated. For extramedullary disease that achieves complete response, PET–CT, MRI, or weight bearing-CT schedule should align with bone marrow aspirate and biopsy for serial MRD monitoring. The criteria used for each response level will follow the uniform IMWG response criteria.[77]

Time-to-event definitions

It is important to provide uniform time-to-event definitions for CAR T-cell therapy. These endpoints have been defined in previous guidelines for patients involved in clinical trials but require modification for patients receiving CAR T-cell therapy.[77] These definitions should be consistent regardless of the clinical scenario in which the CAR T-cell therapies are administered (ie, in front-line therapy, early relapse, and greater than the fourth line). The proposed definitions are listed in panel 4.

Practical considerations

Several practical points must be emphasised regarding response assessment in CAR T-cell therapy. First, patients receiving CAR T-cell therapy for relapsed or refractory multiple myeloma can have very aggressive disease; thus, serial disease assessment throughout the pre-CAR T-cell infusion period is necessary to ensure representative baseline disease assessment and assist with bridging management. After CAR T-cell infusion, free light chain (FLC) clearance can occur rapidly and often precedes M-protein clearance, making calculation of the FLC ratio not possible. This has been found to be prognostic for prolonged progression-free survival, and thus likely behaves similarly to stringent complete response with a

	SPEP	UPEP or urine M-protein in 24 h	SIFE or UIFE*	SFLC (kappa lambda mg/L ratio)	Bone marrow aspirate and biopsy (minimal residual disease and immunohistochemistry)	Radiology (PET, MRI, or CT)	Response assessed (PR and VGPR % change and complete response)
At time of progression or diagnosis (pre-apheresis)†	X	X	X, X	X	X	X	..
After bridging chemotherapy†	X	X	X, X	X	X‡	X	X

M-protein=monoclonal protein. PR=partial remission (>50–90% reduction). SFLC=serum free light chain. SIFE=serum immunofixation electrophoresis. SPEP=serum protein electrophoresis. UIFE=urine immunofixation electrophoresis. UPEP=urine protein electrophoresis. VGPR=very good partial remission (>90% reduction). X=baseline test performed. *Only required at baseline and for assessment of complete response. †Repeat response assessments should be performed pre-leukapheresis, after each cycle of bridging therapy pre-CAR T-cell therapy, and pre-lymphodepletion as clinically indicated. If there is evidence of progressive disease, the multiple myeloma disease burden values at progressive disease become the new baseline for subsequent response assessments. ‡Bone marrow aspirate only required to confirm complete response or if only measurable disease.

Table 2: **Myeloma testing before lymphodepletion chemotherapy**

	All scheduled response assessment timepoints*	At suspected complete response	At suspected progression
SPEP (1 g/dL)†	X	X	X
SIFE	X	X	X
UPEP (200 mg per 24 hrs)	X	X	X
UIFE	X	X	X
Serum free light chain‡	X	X	X
Bone marrow aspirate and biopsies§	X	X	X
Minimal residual disease (next generation flow or next generation sequencing)	..	X¶	..
^{18}F-fluorodeoxyglucose PET¶	X	X	X
Haemoglobin, serum calcium, or serum creatine	X		X

SIFE=serum immunofixation electrophoresis. SPEP=serum protein electrophoresis. UIFE=urine immunofixation electrophoresis. UPEP=urine protein electrophoresis. X=test performed. *Timepoints for assessment=pre-lymphodepletion, day 30, 90, 180, 270, 360, then every 3 months for 3 years. †Measurable disease includes a serum or urine monoclonal protein (M-protein) of 1 g/dL and 200 mg per 24 h, respectively. A baseline M-spike of ≥0·5 g/dL is acceptable, but only very good partial response or higher is measurable and progression-free survival and time to progression. ‡Serum free light chain is used when serum and urine M-proteins are not measurable. §Bone marrow biopsy is used for response assessment when all serum and urine proteins are not measurable and 30% bone marrow plasma cells are present. When used for response assessment, it should be performed every 3–4 months until plateau in response, to confirm suspected complete response or as clinically indicated. When measurable disease is present, bone marrow aspirates are recommended at days 30 or 90, 180, and 360, and to confirm suspected complete response as clinically indicated. The day 30 or 90, 180, 360, and complete response bone marrow aspirates should be used to assess for minimal residual disease status and then yearly bone marrow aspirates can be obtained thereafter to assess for sustained minimal residual disease negativity. ¶With known plasmacytomas, PET imaging should be performed every 3–4 months until plateau in response, to confirm suspected complete response or as clinically indicated. PET imaging can be used in concert with bone marrow aspirate sampling to assess for minimal residual disease.

Table 3: **Myeloma testing following lymphodepletion chemotherapy and CAR T-cell infusion**

normal serum FLC ratio.[78,79] Patients with relapsed or refractory multiple myeloma are more likely to have extramedullary disease pre-CAR T-cell therapy or have extramedullary disease relapse post-CAR T-cell therapy, thus continual imaging monitoring on a serial schedule is recommended (table 3).

Second malignancy

In the KarMMa-3 study, 13 (6%) patients in the ide-cel treatment group and six (5%) in the control group developed secondary cancers within the short follow-up of the trial.[15] Of the 13 patients, nine (69%) had invasive cancer (with solid cancers being slightly more common than haematological cancers), while four (31%) had non-invasive skin cancers. In the CARTITUDE-4 study, nine (4%) patients in the cilta-cel treatment group and 14 (7%) in the control group developed second cancers to date.[16] Among the nine patients, three (33%) had haematological malignancies, including one each for acute myeloid leukaemia, myelodysplastic syndrome, and peripheral T-cell lymphoma. Age-appropriate screening guidelines for all cancers should be followed after CAR T-cell therapy.

On Nov 28, 2023, the FDA announced an investigation into the risk of T-cell lymphoma associated with all six of its currently approved CAR T-cell therapies across all approved indications that include B-cell acute lymphoblastic leukaemia, lymphoma, and myeloma.[80,81] A preliminary analysis reported 12 cases of T-cell lymphoma among 17700 (0·068%) infusions for B-cell malignancies and multiple myeloma. The number of cases of T-cell lymphoma that were CAR+ is not yet reported, although one case is known for cilta-cel.[82] This risk should be discussed with patients, using updated data as they become available, when evaluating the risk versus benefit of CAR T-cell therapy.[83]

Panel 4: **Time-to-event definitions in CAR T-cell therapy**

Progression-free survival
The time from the date of the initial infusion of CAR T cells to the date of first documented disease progression, or death due to any cause, whichever occurs first. Importantly, for patients who have not met official International Myeloma Working Group criteria for progression and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Overall survival
The date of the initial infusion of CAR T cells to the date of the patient's death due to any cause. If the patient is alive or the vital status is unknown, then their data will be censored at the date they were last known to be alive.

Duration of response
The time from first observation of partial response (which might be the date of the initial CAR T-cell infusion for patients receiving front-line, salvage, or bridging chemotherapy before CAR T-cell therapy or the date of partial response post-CAR T-cell therapy, compared with baseline), to the time of disease progression, with deaths from causes other than progression censored.

Disease-free survival
The duration from start of complete response until the time of relapse from complete response. Revised guidelines have provided another definition for disease-free survival for patients who show minimal residual disease negativity (10^{-5} sensitivity). In these patients, disease-free survival can be defined as the time from first achieving minimal residual disease negativity to the time of reappearance of minimal residual disease.

Future directions

Numerous ongoing clinical trials are investigating the use of ide-cel and cilta-cel for front-line treatment. Several allogeneic CAR T-cell clinical trials as potential

off-the-shelf options are in testing.[84] To date, results suggest safety without severe graft-versus-host disease, although the persistence of CAR T cells and durability of response remain a challenge. A more promising strategy to improve patient access to therapy is rapid manufacturing CAR T cells (FasT CAR-T, GC012F, and PHE885).[85,86] Of note, these cells appear functionally more fit and potent than the current conventional CAR-T cells with longer ex vivo manufacturing time, and log-fold smaller doses can be given with compromising efficacy. Academic centre point-of-care manufacturing was also shown to be feasible in a Spanish study with ARI0002H CAR T-cell therapy.[36] CAR T-cell therapy targeting other surface markers (eg, GPRC5D, dual BCMA, and CD19) is also in clinical testing.[87–90]

Contributors

YL and TM performed the primary writing. All authors contributed to the systematic review and data generation, interpretation, and critical review of all the data. All authors contributed to the survey. All authors had full access to and contributed to the final review of this manuscript. YL had final responsibility for the decision to submit for publication.

Declaration of interests

YL received consultancy fees from Janssen, Sanofi, NexImmune, Caribou, Bristol Myers Squibb (BMS), Pfizer, Regeneron, and Genentech; research fees from Janssen and BMS; serves on advisory boards for Janssen, Sanofi, BMS, Regeneron, and Genentech; serves on scientific advisory boards for NexImmune and Caribou; and serves on the data safety monitor board for Pfizer. LQ received consultancy fees from Beigene, Xi'an, Janssen, Pfizer, Sanofi, and AstraZeneca; and is on the speaker board for Beigene, Xi'an, Janssen, Pfizer, Sanofi, AstraZeneca, and Roche. SU receives consultancy fees from AbbVie, Amgen, BMS, EdoPharma, Genentech, Gilead, GlaxoSmithKline (GSK), Janssen, Karyopharm Therapeutics, Merck, Oncopeptides, Sanofi, Seagen, Secura Bio, SkylineDx, and Takeda; and received research funding from AbbVie, Amgen, Array Biopharma, BMS, EdoPharma, Genentech, Gilead, GSK, Janssen, Merck, Moderna, Pharmacyclics, Seagen, Sanofi, SkylineDx, Takeda, and TeneoBio. 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CFdL received institutional grants from BMS, Janssen, and Amgen; honoraria from Amgen, Jassen, BMS, GSK, and Sanofi; support for attending meetings or travel from Janssen, BMS, GSK, and Amgen; is on data safety monitoring or advisory boards for Janssen, BMS, Amgen, Pfizer, and Sanofi; and received funding from the Spanish Institute of Health, the Asociación Española Contra el Cancer (AECC), the "La Caixa" Foundation, and AGAUR. RH received grants from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda; consulting fees from Janssen, Amgen, Celgene, BMS, Novartis, Takeda, AbbVie, PharmaMar, Oncopeptides, Sanofi, and GSK; and honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda. PJH serves on advisory boards (honoraria not accepted) for Antengene, Gilead, iTeos Therapeutics, Janssen, Novartis, and Pfizer. EK received honoraria from Janssen, Pfizer, GSK, and Prothena; and research support to the institution from GSK, Janssen, and Pfizer. 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