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REPLY

Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'

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We appreciate the concerns raised by Teachey and colleagues[1] (Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038.org/nrclinonc.2018.19 (2018)) regarding the information presented in our Review[2], including the fact that the timing and severity of toxicities might vary depending on the chimeric antigen receptor (CAR) construct used, type of cancer, disease subtype, tumour burden, age of the patient, and comorbidities. Indeed, we had acknowledged many of these considerations in our Review[2]. However, a number of differences in the management of CAR T cell-related toxicities that are mentioned by Teachey and colleagues[1] need to be clarified.

Most importantly, the recommendations that we proposed in our Review[2] are for the adult population only. This distinction is crucial because, as discussed by Teachey et al.[1], the profile of toxicities and their management can be very different between children and adults. We had made this point clearly in our article and, again, emphasize that our recommendations are restricted to adult patients. We commend the authors for their extensive experience in administering CAR T cell therapy to paediatric patients, and believe similar guidelines for the management of children would be very valuable.

We also applaud Teachey and colleagues[1] for pioneering the administration of CAR T cell products, such as tisagenlecleucel and JCAR017, in the outpatient setting. To our knowledge, however, this approach has been used at select centres such as the ones that the authors describe — the Children's Hospital of Philadelphia (PA, USA) and the Fred Hutchinson Cancer Research Center (Seattle, WA, USA). It must be noted that, outside these institutions, the vast majority of adult patients with non-Hodgkin lymphoma treated in the multicentre JULIET[3,4] and TRANSCEND[3,4] trials received tisagenlecleucel and JCAR017 as inpatients, and were monitored following infusion in a hospitalized setting. In our experience, sinus tachycardia is generally the first sign of cytokine-release syndrome (CRS) in adults and can precede fever by several hours and sometimes days. We have also observed that the first sign of CAR T cell-related encephalopathy syndrome (CRES) is typically either impaired handwriting or an inability to count numbers backwards, both of which are subtle signs not readily recognizable even by experienced clinicians, unless patients are specifically evaluated using the CAR T cell therapy-associated toxicity 10 point (CARTOX-10) neurological assessment that we proposed in our article[2]. Thus, while we agree that outpatient administration of CAR T cell therapy and subsequent monitoring of patients can be feasible in certain settings, at this time, the experience with this approach has been limited to a few centres with dedicated, highly developed outpatient facilities. We suggest that Teachey and colleagues publish their recommendations on the appropriate monitoring for CRS and CRES when CAR T cell products are administered in the outpatient setting. Importantly, details of the outpatient resources, infrastructure, and procedures required for CAR T cell therapy should be clarified, such as specialized clinics for patient monitoring (including weekend clinics), a triage process for patients presenting to emergency rooms, specialized cell-therapy units with beds readily available in case of emergency admissions, and how long patients need to stay in close proximity to the location where the treatment was administered. Finally, safety outcomes, median time to admission for toxicities, percentage of admissions prevented, median duration of hospital stay, and infrastructure costs for outpatient monitoring must all be considered before determining whether outcomes and costs differ between the inpatient and outpatient approaches.

Teachey et al.[1] disagree with some of our recommendations regarding corticosteroid use for the treatment of both CRS and CRES. As they point out, however, their disagreement is based on their experience in the ELIANA trial[5], which was performed in paediatric and young adult patients (aged ≤25 years) with acute lymphoblastic leukaemia (ALL). First, our recommendations are meant for adult patients and are based on our collective experience with multiple CAR T cell products in adults with non-Hodgkin lymphoma and ALL[3,4,6–8]. Second, the CRS grading used in the ELIANA trial[9,10] has important differences from the modified version of the Lee et al.[11] CRS grading system that we proposed in our article[2]. For example, grade 2 CRS according to our grading system is more severe than grade 2 CRS by the criteria used in the ELIANA trial. Third, while we suggest administration of dexamethasone at a dose of 10 mg every 6 h for the treatment of grade 2 or 3 CRS that is refractory to anti-IL-6 therapy, we also recommend that corticosteroid tapering should be as rapid as possible and individualized depending on the patient's response. Thus, in some patients, dexamethasone can be stopped after one or two doses, if the toxicity resolves, in which case the doses are comparable to methylprednisolone doses of 1–2 mg/kg per day for an average-sized adult. More importantly, in a multicentre study of CAR T cell therapy in >100 patients[6], in which a grade-based management strategy was adopted for CRS and CRES, the use of corticosteroids for severe toxicities did not adversely affect the overall or complete response rates, or the durability of the therapeutic responses.

Teachey and colleagues[1] also erroneously suggest that our management strategy is the same for patients with seizures and cerebral oedema. In fact, we proposed separate algorithms for the management of seizures and cerebral oedema[2]. Contrary to their experience in the paediatric population, we found that in adult patients, anti-IL-6 therapy is effective in reversing CRES that occurs concurrently with CRS[2,6]. As indicated in our article[2], we do not recommend using anti-IL-6 therapy for the treatment of CRES in the absence of concurrent CRS. In addition, Teachey and colleagues[1] incorrectly state that grade 5 neurotoxicity has never been observed with tisagenlecleucel (previously called CTL019). As highlighted in our article[2] and detailed in clinical trial data published in December 2017 by Schuster and colleagues[12], a fatal case of encephalopathy has occurred in a patient with follicular lymphoma treated with CTL019.

We applaud Teachey and colleagues for pioneering the use of tocilizumab for the

management of CRS. In our experience, both tocilizumab and siltuximab have been effective in the initial management of CRS in adults. Nevertheless, we agree that prospective clinical studies are needed to directly compare the effectiveness of tocilizumab and siltuximab in the treatment of CRS, and have made this statement in our article[2]. With the FDA approval of tocilizumab for the management of CRS, which was announced while our manuscript was in press and being prepared for publication online, we agree that tocilizumab is currently the first-line anti-IL-6 therapy of choice for the treatment of CRS.

We also agree with Teachey and colleagues[1] that CRS and haemophagocytic lymphohistiocytosis and/or macrophage activation syndrome (HLH/MAS) have overlapping pathologies and clinical manifestations, and have stated so in our article[2]. Teachey and colleagues[1] correctly point out that most patients with grade ≥2 CRS would meet the published consensus diagnostic criteria for HLH/MAS. Thus, we believe that such criteria are not useful to identify patients who develop 'fulminant CAR T cell-related HLH/MAS', who might need therapy beyond that used for the management of CRS. By contrast, using the diagnostic criteria proposed in our article[2], we have found that fulminant CAR T cell-related HLH/MAS is observed in only ~1% of adult patients treated with CAR T cell therapy[6]. We agree that the treatment of the underlying CRS should be the initial approach to therapy for CAR T cell-related HLH/MAS, and this strategy is reflected in our proposed treatment algorithm[2]. We also agree that a paucity of data exist on the use of etoposide and intrathecal cytarabine in the setting of CAR T cell-related HLH/MAS and have acknowledged this limitation in our article. We accept that the role of etoposide-based therapy has only been clearly established for primary HLH occurring in children; however, published data do suggest that etoposide-based therapies might also be effective in adult patients with HLH, especially in those with cancer-related or infection-associated HLH[13], or those with refractory HLH[14]. For these reasons, we suggested these therapies can be "considered"[2] only when anti-IL-6 therapy and corticosteroids have been tried and found to be ineffective. Despite the prior experience with intrathecal methotrexate in patients with HLH/MAS involving the central nervous system[15], we did not recommend this approach owing to reports of leukoencephalopathy occurring in some patients with CRES after CAR T cell therapy[16,17].

Teachey et al.[1] also disagreed with some minor recommendations we made for supportive care of patients treated with CAR T cells. As suggested in our article, the supportive care strategies that we proposed are "considerations"[2] that can be used when deemed necessary for the management of these patients. Such considerations are likely to improve the safety of CAR T cell administration, and minimize morbidity and, possibly, mortality. Teachey and colleagues[1] incorrectly suggest that we recommend routine use of filgrastim for all patients with neutropenia. We recommended use of filgrastim for patients with neutropenia who develop fever because there is no reliable way to distinguish fever due to infection from fever due to CRS, and an infection that is not treated appropriately in the setting of CRS and neutropenia might have fatal consequences[2]. Teachey and colleagues[1] also incorrectly state that we recommend telemetry during the entire hospital stay: we recommended telemetry only between the day of CAR T cell infusion and the resolution of CRS[2]. We agree with the authors that telemetry might not be necessary for paediatric patients, but adults frequently have underlying heart disease or other risk factors for arrhythmias. Also, as stated in our article[2], hypothermia blankets can be considered, as needed, for the management of fever when antipyretics are not effective. Teachey and colleagues inaccurately comment that we recommend spine MRI for all patients with "focal neurological deficits"[1]. In fact, we recommended spine MRI for patients with "focal peripheral neurological deficits"[2], which usually suggests the presence of a spinal lesion. Lastly, in our experience, there is currently no way to consistently identify patients at high risk of developing convulsive or non-convulsive seizures; therefore, our suggestion is to 'consider' seizure prophylaxis for patients receiving CAR T cell therapies that are known to cause CRES[2], as these patients frequently develop electrographic seizure activity.

In summary, that the grading of CRS and CRES has differed across various CAR T cell therapy trials is important to recognize. Another critical consideration is that our guidelines for the grading and management of CAR T cell-related toxicities are meant for adult patients[2], and not the paediatric population. On the basis of our collective experience using multiple CAR T cell products in adults[3,4,6–8], we modified the CRS grading system reported previously by Lee et al.[11] and proposed a new grading system for CRES that is objective and easy to use. The management strategies that we propose are based on the toxicity grade. In our experience, if the grading of toxicities is performed consistently, the grade-based management strategies we propose can potentially be applied across the various CAR T cell products used in adult patients with cancer. We again acknowledge, however, that the grading and management strategies are likely to change over time as we gain a better understanding of CRS and CRES, and as additional information becomes available from multiple clinical trials. Notwithstanding, the adoption of consistent grading and management strategies is necessary for the systematic and methodical evaluation of data across different studies, and for the field to continually improve toxicity management strategies via an iterative process.

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Competing interests

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