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

David T. Teachey, Michael R. Bishop, David G. Maloney and Stephan A. Grupp

In the January 2018 issue of this journal, Neelapu and colleagues published a Review on the diagnosis and management of the major toxicities associated with chimeric antigen receptor (CAR) T cell therapy, including cytokine-release syndrome (CRS) and neurotoxicity (Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. *Nat. Rev. Clin. Oncol.* **15**, 47–62 (2018))[1]. The authors should be commended for their attempt to develop consensus guidelines on CAR T cell-related toxicities, and we completely agree with many of their assertions, including the notion that CRS is an on-target toxicity of CAR T cells, and the key point that the risk and severity of CRS are typically increased in patients with a high disease burden and/or antigen load. Importantly, the guidelines proposed in the Review were predominately predicated on the authors' experience with axicabtagene ciloleucil (axi-cel), an anti-CD19 CAR construct containing a CD28 co-stimulatory domain, in patients with aggressive forms of non-Hodgkin lymphoma (NHL). Notably, many of these recommendations are not consistent with the published data or our collective clinical experience in treating hundreds of patients with CD19-positive haematological malignancies using T cells expressing CAR constructs containing a 4-1BB co-stimulatory domain. Our concern is that some of the recommendations will place an unnecessary burden on patients and health-care providers, while others might reduce the efficacy of CAR T cell therapy or the ability to safely manage toxicities.

The development of 'universal guidelines' for CAR T cell therapy would be useful; however, the magnitude and timing of the toxicities associated with CAR T cell therapy vary considerably, not only between different CAR T cell constructs, but also across different diseases (acute lymphocytic leukaemia (ALL) versus NHL). Toxicity profiles might also be influenced by multiple other factors, including the characteristics of the patient population, in terms of age and co-morbidities, as well as prior therapy. Tisagenlecleucel was approved by the FDA in August 2017, and axi-cel was approved in October 2017. At present, tisagenlecleucel is indicated only for the treatment of children and young adults (aged ≤25 years) with relapsed or refractory B cell ALL (B-ALL), whereas axi-cel is approved for use in adults with certain relapsed and/or refractory large B cell NHLs. Of note, multiple studies using conventional chemotherapy have established that the risk of toxicity increases with patient age[2,3]. Similarly, after CAR T cell therapy, children might be less likely than adults to have short-term or long-term CRS-related morbidity and/or mortality. Thus, many of the recommendations proposed by Neelapu et al.[1] for the management of mild to moderate CRS are not necessarily relevant in children. Importantly, however, the rates of grade 3–4 CRS are higher in patients with B-ALL than in those with NHL. For example, the rates of grade 3–4 CRS (using the Penn CRS grading scale[4]) in the ELIANA registration trial[5] of tisagenlecleucel therapy for paediatric and young adult ALL and in the JULIET registration trial[6] of the same agent for the treatment of adult NHL were 48% and 26%, respectively.

Neelapu and colleagues[1] also suggest that patients need to be hospitalized and monitored for at least 7 days after CAR T cell infusion. This precautionary approach was required in the clinical trials of axi-cel, but we have not found this to be necessary in studies using CAR T cell constructs containing a 4-1BB co-stimulatory domain, including tisagenlecleucel, JCAR014, and JCAR017, in both ALL and NHL populations. Fever is typically the presenting symptom of CAR T cell-associated CRS (at least with 4-1BB CAR T cells), with critical illness arising 12–96 h later, if at all[7–12]. Patients can therefore be infused with CAR T cells in the outpatient setting and admitted to hospital at the time of fever development. This strategy does require careful monitoring for symptoms by caregivers and the patients themselves during the outpatient period. Fever most frequently occurs within 5–7 days after infusion, although late fevers rarely occur after around 2–3 weeks and might not represent CRS; the label for tisagenlecluecel suggests a 4-week monitoring period. Using this approach, some patients, especially those with a low disease burden, do not require hospital admission at all. In fact, the large majority of CAR T cell infusions performed at the Children's Hospital of Philadelphia (PA, USA) or at the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) occur in the outpatient setting. Again, we emphasize that the CAR T cell constructs used at these institutions are different from others used elsewhere; these differences, together with other dissimilarities related to the disease context, might lead to variability in the risks and timing of toxicities. Thus, although some CAR T cell products or patient populations might warrant anticipatory hospital admission, we believe that hospitalization of all patients treated with CAR T cells is not necessary. A blanket approach to mandating inpatient infusion would increase costs without necessarily increasing safety and would pose a potential barrier to treatment.

We completely agree with the authors' statement that corticosteroids should be reserved for patients with CAR T cell-related adverse events that are refractory to anti-IL-6 therapy[1]; however, we disagree with some of their guidelines for steroid use. The authors recommend that patients with grade 2 or 3 CRS (using the Lee CRS scale[13]) receive intravenous dexamethasone at a dose of 10 mg every 6 h, and that those with grade 4 CRS receive intravenous methylprednisolone at 1 g per day. In our experience, patients with CRS that is refractory to IL-6 blockade do need corticosteroids, but respond to far lower doses of methylprednisolone. High doses of corticosteroids could potentially reduce the efficacy of CAR T cell therapy; therefore, we recommend and have considerable experience with doses starting at 1–2 mg/kg per day, to which the vast majority of patients requiring steroids respond[5]. The authors also recommend that patients with grade 2 neurotoxicity without concurrent CRS or CRS that is refractory to anti-IL-6 therapy receive the same high-dose steroid regimen proposed for the management of refractory grade 2 CRS[1]. They define grade 2 neurotoxicity as a moderate degree of neurological impairment without seizures, motor weakness, or evidence of raised intracranial pressure[1]. No patient treated with tisagenlecleucel has developed grade 5 neurotoxicity, and patients treated with this agent recover from neurotoxicity with supportive care alone[5]. Thus, we do not recommend the use of empirical corticosteroids for low-grade neurotoxicity. Even with higher-grade neurotoxicity, treatment decisions should be tailored to the type of neurotoxicity, taking into account the features of the CAR T cells received. For example, seizures that are well controlled with anti-epileptic drugs should not be treated in the same way as increased intracranial pressure and cerebral oedema. However, fatal neurological events have occurred with some

CAR T cell products[14], and thus the threshold for corticosteroid use will vary based on the product used and patient population. Finally, our experience is that anti-IL-6 therapy is often not effective for neurotoxicity[5]; thus, using response to IL-6 blockade to determine the next line of therapy might be unwarranted.

Neelapu and co-authors[1] also suggest that tocilizumab and siltuximab are interchangeable for the initial management of CRS. We believe that this recommendation is not supported by clinical trial data from across the field of CAR T cell research to date, necessitating further studies to establish the comparative effectiveness of these agents. Tocilizumab is now approved by the FDA for the management of severe CRS based on extensive clinical data demonstrating the efficacy of this agent in the majority of patients[8,9,11–13,15]. Siltuximab has not been studied as a first-line therapy for CRS and is not currently FDA-approved for this indication. The approach we have used in CHOP and University of Pennsylvania trials has been to use siltuximab as third-line treatment for CRS, after failure of both tocilizumab and corticosteroid therapy. We believe that this is the best approach until clinical trials of this agent are performed in the first-line setting.

We also disagree with the description and management of haemophagocytic lymphohistiocytosis and/or macrophage activation syndrome (HLH/MAS). CRS and HLH/MAS have pathologies that overlap substantially: most patients with grade ≥2 CRS meet the published consensus diagnostic criteria for HLH/MAS[16], and most patients with grade ≥3 CRS meet the definition of CAR T cell-related HLH/MAS proposed by Neelapu and colleagues[7]. This observation is in striking contrast with the authors' statement that HLH/MAS is observed in only ~1% of patients treated with CAR T cells[1]. The authors suggest that treatment with etoposide and intrathecal cytarabine can be considered for CAR T cell-related HLH/MAS that has not improved after 48 h of therapy for CRS. Early use of etoposide and intrathecal cytarabine for HLH/MAS arising after CAR T cell infusion is entirely speculative. Etoposide is indicated for patients with genetic primary HLH and is not needed in many patients with secondary HLH/MAS, regardless of the cause[17]. In addition, destruction of the CAR T cells by etoposide is an obvious concern. The intrathecal chemotherapeutic of choice, and the only one systematically studied in patients with HLH, is methotrexate[18]; a paucity of published data currently exist regarding the use of intrathecal cytarabine for the treatment of any form of HLH/MAS. We are definitely not suggesting that intrathecal methotrexate be used for CAR T cell-associated HLH/MAS (we advocate treatment of the underlying CRS to manage HLH/MAS), but rather wish to highlight the fact that no existing data indicate that cytarabine is an active drug for any form of HLH/MAS.

On the basis of our experience with CAR T cell therapy, we disagree with a number of minor recommendations made by Neelapu et al.[1], and particularly their applicability to the paediatric and young adult population. First, we have not routinely used filgrastim to treat all neutropenic patients, although the requirement for this agent might differ between adult and paediatric populations. Second, we have not monitored paediatric or young adult patients, or those with a low disease burden, using telemetry during their entire hospital stay. Third, we do not routinely use a hypothermia blanket for febrile patients. Fourth, we do not obtain spine MRIs for focal neurological deficits except in cases where the deficit would suggest a spinal lesion. Finally, we do not recommend seizure prophylaxis with levetiracetam for 30 days starting the day of infusion in all patients. We agree that these interventions are beneficial for a subset of patients, but they might not be necessary with all CAR T cell products and should not be applied universally to all CAR T cell-treated patients. We reserve filgrastim for neutropenic patients with confirmed bacterial infection; use routine cardiac monitoring, rather than telemetry, for the vast majority of patients; and prescribe prophylatic levetiracetam only for patients with a prior history of central nervous system (CNS) toxicity, CNS co-morbidity, or CNS leukaemia at the time of CAR T cell infusion and for patients who develop neurotoxicity.

In summary, we applaud the authors for developing a working group to develop consensus recommendations for the toxicities associated with CAR T cell therapy; however, we believe that many of the recommendations should not be applied universally to all CAR T cell products and all patients, and that more studies and a consensus conference are needed to develop standard practice guidelines that will be applicable to the two currently approved CAR T cell therapies

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