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WHAT'S NEW IN INTENSIVE CARE

Acute life-threatening toxicity from CAR T-cell therapy

Elie Azoulay*, Michael Darmon and Sandrine Valade

Chimeric antigen receptor (CAR) T-cell therapy is an effective adoptive cell treatment that constitutes a powerful new class of therapeutic agents to treat patients with B-cell leukemia and lymphoma [1]. It uses patient's T lymphocytes harvested through cytapheresis and manipulated ex vivo to express specific antigens before infusion back to the patient. Although the clinical responses are beyond expectations, CAR T-cells also frequently produce life-threatening acute toxicities [2], chiefly the cytokine-release syndrome (CRS) and neurotoxicity (Fig. 1). Tumor lysis syndrome that has been reported in up to 5% of the patients in the first trials, is not discussed in this short article. Obviously, in these high risk immunocompromised patients with altered B cell and T cell response and frequent neutropenia, sepsis should be ruled out and treated empirically. In this what's new paper, we have listed the top ten tips to manage critically ill CAR T-cell recipients.

Learning from oncology

Many ICU specialists are used to manage the toxicity of checkpoint inhibitors that allow the potentiation of T-cell specific immune responses against tumor cells. Uncontrolled multi-organ immune-related adverse events occur rarely with checkpoint inhibitors [3], but life-threatening toxicity affects 1% of the treated patients [4] and management share common points with CAR T-cell-related toxicity. Namely, (1) early resuscitation; (2) careful clinical examination to assess severity and rule out infection; (3) empirical antibiotics; (4) close collaboration with oncologists and hematologists and (5) anti-inflammatory therapy, mostly relying on steroids.

*Correspondence: elie.azoulay@aphp.fr
Médecine Intensive Et Réanimation, APHP, Hôpital Saint-Louis, Paris Diderot Sorbonne University, Paris, France

CAR T-cell Therapy: the miracle from adoptive immunotherapy

Currently, two types of anti-CD19 CAR T-cell therapies (tisagenlecleucel and axicabtagene-ciloleucel) are available for B malignancies. Impressive short and longer term outcomes have been reported [5–7]. CAR T-cells recipients are patients refractory to several lines of chemotherapy, and sometimes stem cell transplantation. Yet, more than half the patients have progression-free survival at 1 year [5–7] and longer term survival is close to 50%, most particularly with the second generation CARs [8].

Rule out sepsis

Unsurprisingly, CAR T-cell recipients are at high risk of sepsis. In a study including 133 patients, Hill et al. reported infectious episodes within 28 days after infusion in 23% of the patients (1.19/100 days) [9]. A second study reported that 22/53 patients (42%) presented with infections within 30 days after infusion [10]. Most infections are diagnosed within 10 days after CAR-T cells infusion (median 6 days). Severe CRS was independently associated with infection [9] with up to 50% of patients with severe CRS developing documented bloodstream infections [10]. These high risk immunocompromised and mostly neutropenic patients should routinely receive broad spectrum empirical antibiotics.

Cytokine Release Syndrome: the most common acute toxicity

The endothelium and myeloid cells are central in CRS development and severity. Once CAR T-cells interact with tumoral B-cells, they become activated and expand, with a cytokine release (mostly IFN-γ and TNF-α) resulting from cell lysis. Furthermore, monocytes and macrophages also enhance tumoricidal capacity and their activation results in the production of high levels of pro-inflammatory cytokines (IL-6, IL-1, IL-10) resulting

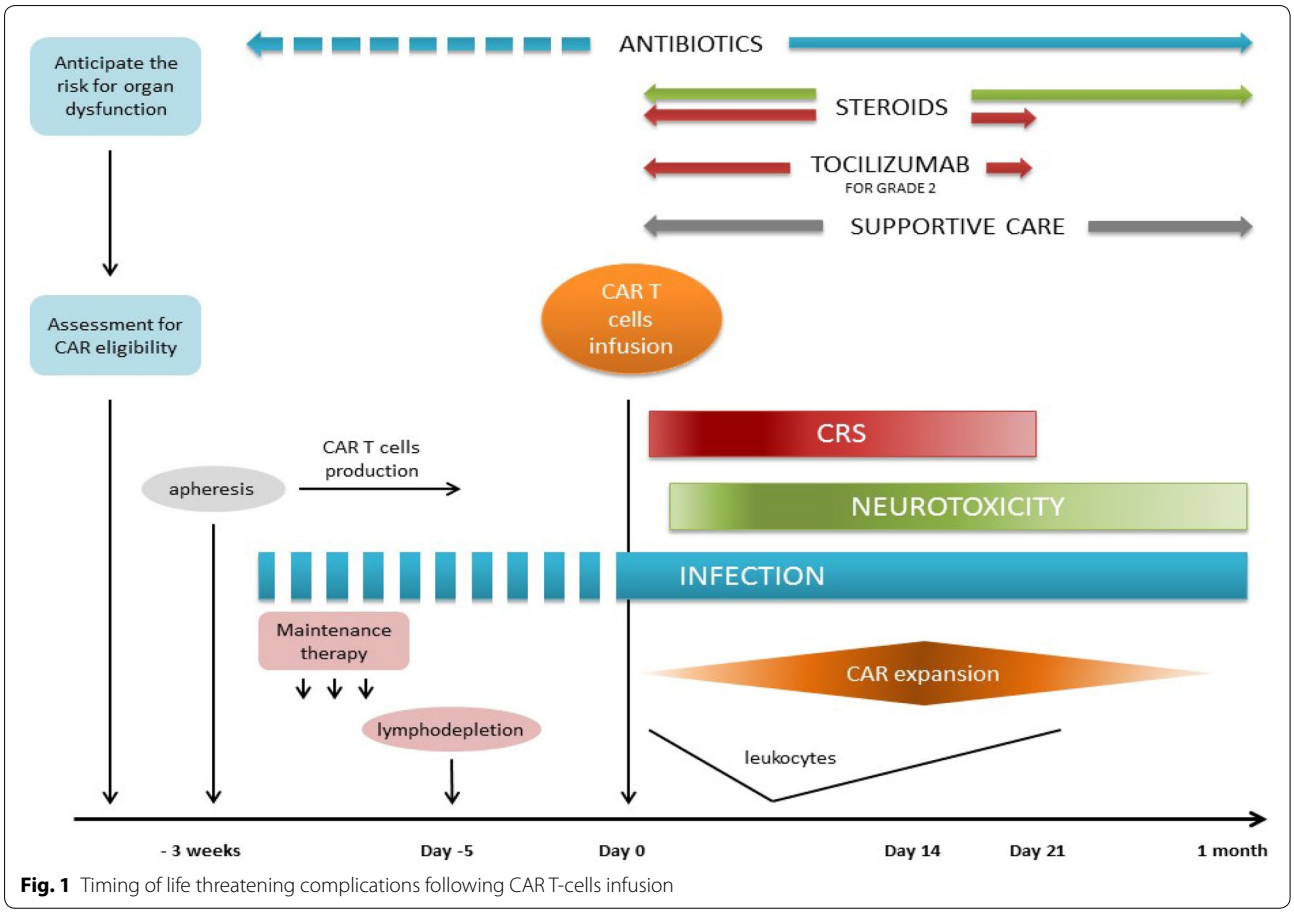

Fig. 1 Timing of life threatening complications following CAR T-cells infusion

in CRS progression [2, 11, 12]. CRS is related to CAR-T expansion in vivo and anti-tumoral activity [11, 12]. One in four patients will present severe CRS (need for vasopressors or high flow oxygen) [2, 11], with higher rates in patients with B-ALL (29.3%) as compared to those with B-lymphoma (19.8%) [13]. Risk factors for severe CRS include high disease burden, high infusional dose, fludarabine containing lymphodepletion, concomitant infection, and fractionated dosing schemes [13].

Patients present a flu-like syndrome (fever, myalgia, fatigue, nausea, diarrhea) within 1 to 14 days following CAR infusion. CRS can progress to vasodilatory shock with capillary leak, hypoxemia, and multiple organ failure. The most severe CRS patients may have features of hemophagocytic lymphohistiocytosis (elevated INF-γ, soluble IL-2 Rc, IL-6 and IL-10).

Neurotoxicity

Acute neurologic toxicities occur within 8 weeks following CAR infusions and last for about 2 weeks [2, 11, 12]. This complication also called Immune effector Cell-Associated Neurologic Syndrome (ICANS) is the second most-common adverse event, and can occur with or after CRS. The peak incidence is 4–6 days after infusion and about 20% of patients will present severe neurotoxicity. Headaches, memory loss, dizziness, alterations in mental status (somnolence, disorientation, impaired attention, agitation, coma), movement disorders (tremor, myoclonus), impaired speech (dysartria, aphasia), and seizures are the most frequent signs [5–7]. Neurological involvement can be assessed clinically using the CAR-TOX or the ICE score [11]. EEG may document subclinical seizures, and MRI shows reversible common pattern of T2/FLAIR hyperintensities in 30% of the patients with neurological signs [2, 14, 15].

Two patterns of neurotoxicity differ, although sometimes overlapping. One occurs immediately after CRS and may be related to a dysfunction of the blood brain barrier driven by cytokine production (TNF-α, IL-6 and IL-1), and angiotensin 1/ angiotensin 2 balance, with brain vascular pericyte stress and secretion of endothelium-activating cytokines in a context of early onset or severe CRS [15]. The other one is associated with expansion and activation of CAR T-cells that lead to a direct parenchymal CAR T-cell infiltration. In an animal model, Taraseviciute et al. describe pan-T encephalitis with CAR

and non-CAR T-cell infiltration in the CSF and in the brain during neurotoxicity, accompanied by increased levels of pro-inflammatory cytokines in the CSF [16].

Treatment of CRS

CRS resolution usually occurs within 3 weeks after CAR infusion. According to severity, CRS may require ant-cytokine-directed therapy (tocilizumab or corticosteroids). In patients with isolated fever, close monitoring, paracetamol, and a diagnostic workup to rule out infection should be implemented. Thus, despite their lack of impact on tumor response or CAR expansion, anti-cytokines in early CRS probably constitutes an unnecessary exposure. In patients with low flow oxygen or need for fluid expansion (Grade 2), the decision relies on the pre-test probability of CRS versus sepsis, knowing that the two may be concurrent [9, 10]. We believe that this situation is exactly the place for tocilizumab. In case patients remain febrile without worsening organ dysfunction, tocilizumab could be repeatedly injected.

In patients with severe CRS that is similar to septic shock ($\geq$ Grade3, with vasopressors, high flow oxygen or intubation), tocilizumab may not be indicated anymore and corticosteroids should be started. In patients with refractory multiple organ dysfunction, rescue strategies such as anakinra (human interleukin 1 receptor antagonist), plasma exchange, or hemofiltration have been anecdotically proposed but not evaluated.

Treatment of neurotoxicity

At earliest stages, in patients with mild clinical signs, a complete diagnostic workup to rule out infection and epilepsy, aspiration prevention, seizure prophylaxis with levetiracetam should be implemented. In patients with associated CRS, tocilizumab should be avoided. In sicker patients with depressed level of consciousness, dexamethasone (10 mg q 6 h) should be added and seizures need to be ruled out and controlled. In the sickest patients who are unarousable, with status epilepticus, motor weakness or diffuse cerebral edema, or when brain MRI identifies focal or diffuse edema, 1000 mg of solumedrol should be started. Anakinra has been anecdotically tested.

Avoiding adding toxicity to toxicity

Delay in appropriate antibiotic therapy, in admission to the ICU or suboptimal management of organ dysfunction in the wards can be detrimental. In addition, tocilizumab may deserve to be avoided in selected patients. In patients with mid neurological symptoms and CRS, tocilizumab has been associated with neurological deterioration, which is in line with experimental data showing that the accumulation of IL6 in the intracellular space may be detrimental [17, 18]. Siltuximab that blocks IL6 itself might be an alternative. However, early corticosteroids use does not hamper CAR expansion or tumoral response and might be the drug of choice in these patients.

New CAR T-cells

Third-generation CAR T-cells will be able to produce lower levels of cytokines, express higher levels of antiapoptotic molecules and proliferated more slowly than exisiting CARs, resulting in minimal rates of CRS and neurotoxicity, still with potent cytolytic activity [19]. Similarly, GM-CSF neutralization with lenzilumab does not inhibit CART19 cell function in vitro or in vivo, yet CAR proliferation is durable and anti-tumoral activity persists [20].

The role of ICU specialists for the management of acute toxicities of CAR T-cell therapy

We believe that the role of intensivists is crucial at different stages of the CAR T-cell process. Once patients are assessed for CAR eligibility, ICU specialists may help anticipate the risk for developing organ dysfunction or sepsis, based on patient's frailty, immunity and comorbid conditions. Before CAR infusion, maintenance therapy that allowed to wait for CAR T-cell therapy and lymphodepletion are adding specific risks factors for acute toxicity [2, 12], that need a clinical update with intensivists. After CAR infusion, when patients develop subacute fever and mild organ derangement, we strongly support early ICU admission. Studies to validate algorithms for thresholds for involving the intensivist and admission to ICU are warranted.

Compliance with ethical standards

Conflicts of interest

Over the last 3 years, EA received honoraria or travel expense reimbursements from Alexion, Baxter, MSD, Ablynx, Pfizer, and Gilead. His hospital received research support from Gilead, Fisher & Payckle, Jazz Pharma, Ablynx, Baxter, Alexion, and Astellas. MD received consulting fees from Sanofi and Gilead-Kite, research support from Astute Medical and MSD, and speaker fees from MSD, Gilead-Kite and Astellas. SV received honoraria from Sanofi (teachings) and Pfizer (invitation to congress).

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