

Effects of cytokine-release syndrome: CNS toxicity and impact on CAR T cells

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I am frequently asked, “How does cytokine-release syndrome (CRS) affect end organs?” Cytokine-release syndrome is an inflammatory condition that leads to fever, hypotension, and, in severe cases, hypoxia. The severe hypotension can be such that patients require pressers in addition to massive IV fluid administration. These are the most common aspects of CRS. Sometimes, it can also involve CNS toxicity where the patient develops altered mental status, and thus it is critically important where these patients are being evaluated, that they are evaluated frequently for mental status changes. Sometimes, these can be very subtle where the patient just is not thinking properly. This can lead to a recognition (often by the caregiver) that something is not right; the family member will come in with the patient and say they are not thinking properly. So, those patients may require lumbar puncture after a CT scan or MRI of the brain to make sure there is nothing else going on. We do not know a lot about this, but we do know that it can be easily treated if recognized early with high dose steroids after tocilizumab treatment. The thing that is interesting about the CNS toxicity is tocilizumab is an antibody and does not cross the blood brain barrier, and because of that we sometimes have to think about other strategies such as using siltuximab. Siltuximab physically binds IL-6 and keeps it from, hopefully, crossing into the brain, or Anakinra which is the interleukin-1 receptor antagonist which has also been shown to have some benefit for CNS toxicity that is not responding well to steroids. Hopefully with early treatment, we do not need to have all these aggressive interventions and that with early intervention with tocilizumab and steroids, we can prevent these toxicities.

I am frequently asked if the treatment for CRS will have a negative impact on the CAR T cells, and we have found no evidence to that effect so far. Initially, people were concerned that steroids would make the lymphocytes go away because CAR T cells are T cell lymphocytes, but that does not seem to be the case. It seems very hard to kill these things off. Steroids are not something to be withheld if the patient is developing rapidly progressive CRS. The initial treatment still remains tocilizumab and that appears to have no impact. People are studying whether or not it can be given prophylactically even before the T-cells go in but we do not know enough about that yet.