

ADVANCES IN LLM

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Optimizing Administration of CAR T-Cell Therapy During the COVID-19 Pandemic



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H&O What are the goals of the CAR T-Cell Consortium?

MB The initial aim of the CAR T-Cell Consortium was to evaluate real-world experience with commercial chimeric antigen receptor (CAR) T-cell products, both axicabtagene ciloleucel (Yescarta, Kite) and tisagenlecleucel (Kymriah, Novartis). The objectives of the consortium have expanded beyond the original goal, and now encompass scientific questions relative to the various products and outcomes in patients. The consortium is currently exploring the possibility of conducting clinical trials. The group of academic institutions that make up the consortium includes the University of Pennsylvania, the University of Chicago, Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, the University of Kansas, the University of Minnesota, Vanderbilt University, and Oregon Health & Science University. Several other institutions have also asked to join. Initial reports from the consortium have drawn some interest because they are the first to compare axicabtagene ciloleucel vs tisagenlecleucel. There have been other reports of real-world experience, but no direct comparative studies at institutions that use both products.

H&O Does the consortium recommend that treatment with CAR T-cell therapy continue during the COVID-19 pandemic?

MB It does, with qualifications. Early in the pandemic, in March, we foresaw the tremendous challenges ahead.

At our institution, we have changed one aspect: the treatment is now administered solely on an inpatient basis.

One such challenge was the availability of anticytokine therapy, specifically tocilizumab (Actemra, Genentech). Administration of CAR T-cell therapy requires access to drugs such as tocilizumab. Early data from both Chinese and Italian groups suggested that tocilizumab could alter the clinical course of coronavirus disease 2019 (COVID-19), especially in patients with severe respiratory problems. This treatment can be lifesaving for both a patient treated with CAR T-cell therapy and a patient with severe respiratory symptoms from COVID-19. Although tocilizumab is a readily available drug, a large uptick in demand could cause shortages. In the case of a shortage, the choice of which patient should receive treatment with tocilizumab would pose an ethical dilemma.

There were several other practical issues to consider. The potential toxicities of CAR T-cell therapy require the availability of a medical intensive care unit (ICU). Early on in the pandemic, services such as interventional radiology and general radiology were limited to protect both

staff and patients. Administration of CAR T-cell therapy should be restricted if it is not possible to place a central line in a patient. X-rays or positron emission tomography scans might be needed to determine disease status. There may be limitations to outpatient resources.

It is also necessary to protect patients and their families. How can we get patients into the hospital safely and protect them from potential infection with the coronavirus? As anticipated, patients have been concerned that a trip to a medical center could expose them to the virus. It is also necessary to determine proper follow-up in the outpatient setting.

In April, the CAR T-Cell Consortium published a statement addressing 7 major questions about coronavirus in *Biology of Blood and Marrow Transplantation*, the journal of the American Society of Transplantation and Cellular Therapy (ASTCT). The statement underwent rapid peer review, as well as review by the president of ASTCT and the Editor-in-Chief of the journal. It appears on the ASTCT website and app.

H&O What are the factors that influence whether a patient should receive CAR T-cell therapy during the pandemic or whether it should be deferred?

MB There are several factors. It is important to consider how aggressive the patient's lymphoma is. We might delay administration of CAR T-cell therapy in a patient whose disease can be maintained with bridging therapy. In contrast, we would proceed with CAR T-cell therapy if bridging therapy failed to keep the disease under control. CAR T-cell therapy might be delayed in a patient with significant medical problems that confer an extremely high risk for cytokine release syndrome or neurotoxicity. These adverse events necessitate the need for admission to a medical ICU or neuro-ICU, which might have limited beds during the pandemic.

Another important factor is the patient's supportive care. In many instances, the caregiver for a patient receiving CAR T-cell therapy is a family member or friend who must travel across the country. The caregivers might have travel-related impediments or medical problems that prohibit them from providing adequate care.

It is a complex issue. When selecting patients for administration of CAR T-cell therapy during the pandemic, we have been giving higher priority to those with more aggressive disease, who were otherwise healthy, and who have proper support from a caregiver.

Fortunately, in most of the cities where our consortium members practice, the state of resources was less dire in the early days of the pandemic than it could have been. The exception was New York City, where there was tremendous stress placed upon the healthcare system,

particularly medical ICUs. The ability to administer CAR T-cell therapy in New York City differed from other cities. For example, Texas had a fair number of COVID-19 patients, but Houston still had availability of medical ICU beds. In Chicago, we had a substantial number of patients with COVID-19. However, there were enough medical ICU beds and ventilators to allow treatment of scheduled CAR T-cell patients, although in a limited manner.

As of early June, the situation has apparently plateaued or improved. We are now administering CAR T-cell therapy to the many patients whose doses were delayed. The difficulty is that there is now a large influx of patients. We are not sure of what to do if there is a second wave of COVID-19. However, we have learned that the situation is fluid, and we have been able to adapt day by day. As the CAR T-Cell Consortium emphasized in the published statement, communication is key within each program, as well as with the patient and the referring physician. It is essential to keep everyone up to date regarding the overall treatment plan.

Testing for coronavirus is administered to all patients, from 24 to 72 hours before they are scheduled to begin lymphodepleting chemotherapy.

H&O What are some of the challenges in obtaining CAR T-cell products during the pandemic?

MB Fortunately, obtaining CAR T-cell products has been less difficult than anticipated. The first consideration was whether there would be enough nurses, particularly apheresis nurses, to perform the procedure. Luckily, apheresis is not needed very much beyond the stem cell transplant and cell therapy settings. Less commonly, apheresis is needed for uses such as collecting plasma and platelets. However, most centers have adequate blood banks, so use of apheresis for these purposes was not a limiting factor. Adequate staffing for apheresis was not an impediment to treatment.

The second concern was transportation of the CAR T-cell product. These products are shipped by airplanes. In the United States, most production sites are on the east

and west coasts. One of the sites of production is in New Jersey, which has an extremely high rate of COVID-19. It was not known early on if staffing would be adequate to maintain production. Fortunately, production has been relatively good; total disruption has not occurred.

In addition to the commercial products used for CAR T-cell therapy, there are research products. The pandemic has blunted several aspects of research. Most clinical trials require many blood samples and multiple tests. At my center and others, staff has been furloughed under a stay-at-home order, so they are not able to properly manage patients enrolled in trials.

Therefore, on the commercial side, there has been minimal interruption in the production of CAR T-cell therapy. On the research side, production has been severely interrupted. Currently, however, many institutions are bringing staff back. Studies that were placed on hold because of the pandemic are starting to open up again.

H&O What are some of the challenges posed by the administration of CAR T-cell therapy to patients during the pandemic?

MB The initial barrier involves physical logistics: setting up clinics in a way to protect patients, ensure social distancing, and arrange adequate staff for assessment. At each visit, these patients must be pre-assessed to ensure that their tests are up to date. Before a patient is admitted, we test for the coronavirus.

Before the pandemic, a caregiver was permitted to stay with the patient throughout administration of therapy. Many transplant and cell therapy units now allow visitors only when absolutely necessary, such as when the patient has certain physical or mental needs or is facing a life-threatening situation. My center and others have adapted to this initial barrier.

The second barrier is to ensure adequate staffing and a protected environment for transplant and cell therapy during the inpatient stay. At my center, we have installed physical barriers to limit foot traffic across units. For example, rooms have one door in and another door out. Everyone who enters into the unit must be identified. Nonessential people are prohibited from entering. When possible, team rounding is limited to one person. This approach limits the number of people patients will have contact with. We also ensure there are enough beds in the medical ICU and neuro-ICUs if patients develop complications.

Once the patient leaves the hospital, he or she needs adequate housing. Some of our patients travel up to 12 hours to the clinic, and they therefore need a place to spend the night. There needs to be a nearby hotel where

the staff practices good techniques to minimize transmission of the coronavirus.

H&O Did other areas at your institution adapt to meet the demands of the epidemic?

MB An amazing aspect of practicing medicine during this pandemic has been to see that there have been few barriers for people who are designing and implementing plans together. There has been a collaborative effort across every line of the healthcare profession, including cleaning, food services, pharmacy, radiology, and nursing. We have even adjusted the ventilation of the rooms to minimize risk.

H&O Should the protocol for the administration of CAR T-cell therapy be altered during the pandemic?

MB In general, the administration should not be altered, so that the potential efficacy can be maintained. At our institution, we have changed one aspect: the treatment is now administered solely on an inpatient basis. We do not want the patient going back and forth to the hospital. At the beginning of the process, patients are admitted to the hospital. They stay in the hospital the entire time, including during administration of lymphodepleting chemotherapy, until they are ready for discharge. We have not changed the regimen for lymphodepleting chemotherapy. If a patient develops cytokine release syndrome, we administer tocilizumab in the standard manner.

H&O What is your testing procedure?

MB Patients undergo standard tests, such as a cardiac workup, pulmonary workup, chemistry tests, and complete blood count. Testing for infection now includes the coronavirus. Testing for coronavirus is administered to all patients, from 24 to 72 hours before they are scheduled to begin lymphodepleting chemotherapy. The administration of CAR T-cell therapy severely alters the patient's immune system, making him or her more vulnerable to potential complications of COVID-19. Therefore, we would not start CAR T-cell therapy in a patient who is potentially infected with coronavirus.

H&O What should be done if a patient who presents for CAR T-cell therapy tests positive for COVID-19?

MB Patients without symptoms are quarantined at home. We repeat the testing. We instruct the patient to

immediately return to the center if there are any changes in signs or symptoms. They would then be admitted for observation and treatment.

Patients who develop COVID-19 during their hospitalization for administration of CAR T-cell therapy pose other challenges. It can be difficult to distinguish whether respiratory symptoms are caused by COVID-19 or the CAR T cells. In general, we would manage these patients according to the most likely etiology of their symptoms. Fortunately, this circumstance has not yet arisen at our institution. I have heard of a few cases around the world. The numbers are so low likely because of the prescreening process.

H&O Are there any strategies to manage patients who had to miss doses of CAR T-cell therapy during the pandemic?

MB We had patients with appointments in April that were delayed. We considered whether these patients could receive bridging therapy to hold their disease in check until administration of CAR T-cell therapy. In these patients, the treatment plan was altered by increasing the cycles of bridging therapy from 1 or 2 to 3 or 4. This change was made in close consultation with the patient's referring oncologist.

H&O Do you have any other observations to share regarding the treatment of patients during the pandemic?

MB Clinicians have been very fair about the allocation of resources. It is remarkable to see such a high level of teamwork among clinicians, not only at our institution, but also among doctors in the CAR T-Cell Consortium. During our conference calls, everyone has been highly empathetic, sympathetic, and cooperative. Nobody thinks

they have the perfect answer. There is a lot of listening. It has been humbling to see this level of collaboration and empathy for each other's situation. That is one of the good things to come out of this situation.

Disclosure

Dr Bishop has received honoraria from Celgene, OptumHealth, and Kite/Gilead. He is a member of the speakers bureaus of Celgene, Kite/Gilead, Agios, Incyte, and Sanofi. He is an advisory board member or a consultant of Juno Therapeutics, Kite/Gilead, Novartis, CRISPR Therapeutics, and OptumHealth.

Suggested Readings

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