The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies

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Joshua Richter: Hello, and welcome to our podcast provided by MediCom Worldwide. Today we're going to be talking about the role of the Emergency Department in treating of multiple myeloma in the era of novel immunotherapies. My name is Dr. Joshua Richter. I'm an Associate Professor of Medicine at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, and the Director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mount Sinai. I'm joined today by two amazing colleagues. I'll have them introduce themselves. The first is the illustrious Dr. Monica Wattana.

Monica Wattana: Hi, everybody. Thank you so much for joining. I am a board-certified emergency medicine physician, and I am an Associate Professor and Director of Education at the University of Texas MD Anderson Cancer Center.

Larysa Sanchez: Hi everyone. My name is Dr. Larysa Sanchez. I am an Assistant Professor of Medicine at the Icahn School of Medicine at Mount Sinai here in New York City.

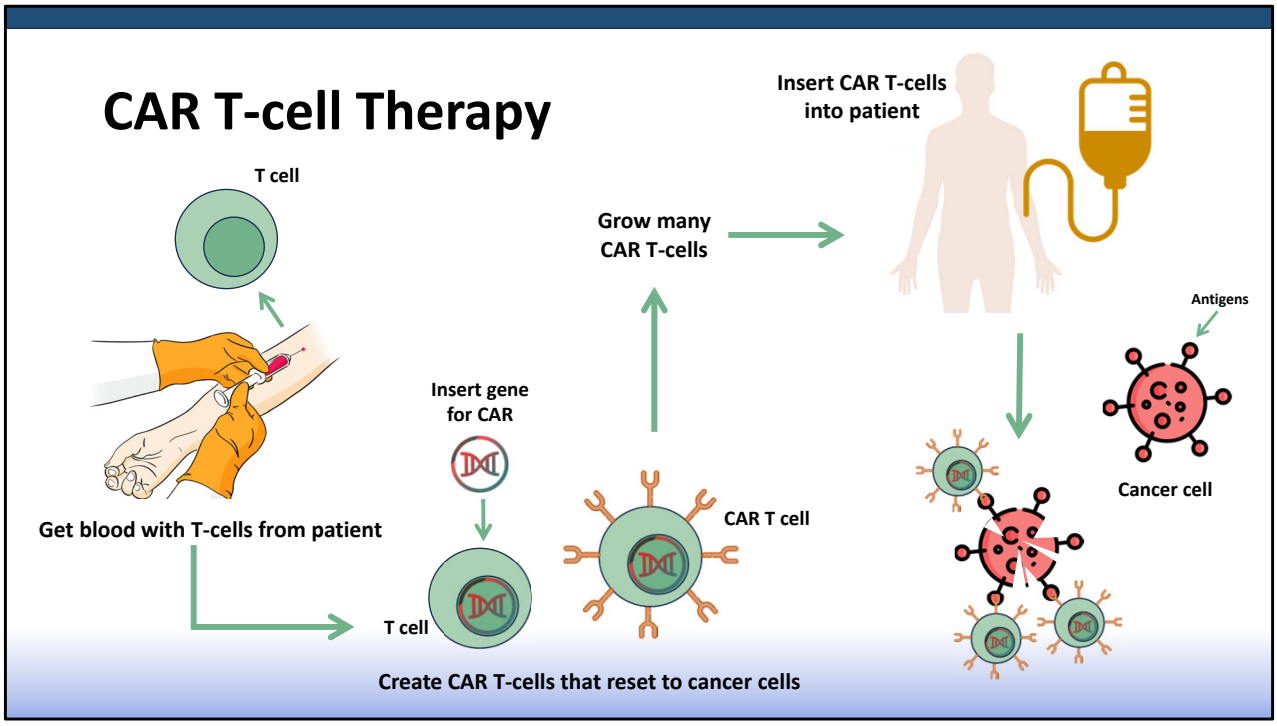
Joshua Richter: This is a companion podcast to our accredited activity. In this podcast, we'll talk about practical applied strategies in the Emergency Department that clinicians can use to treat adverse events which may occur in patients who are being treated for multiple myeloma with some of our novel immunotherapies such as bispecific antibodies and CAR T therapies. If you haven't viewed our accredited video yet, you can use the link below and I encourage you to do so, as it's an important discussion of novel treatments for multiple myeloma and potential treatment-related adverse events, especially those that you might see in the emergency department.

The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies

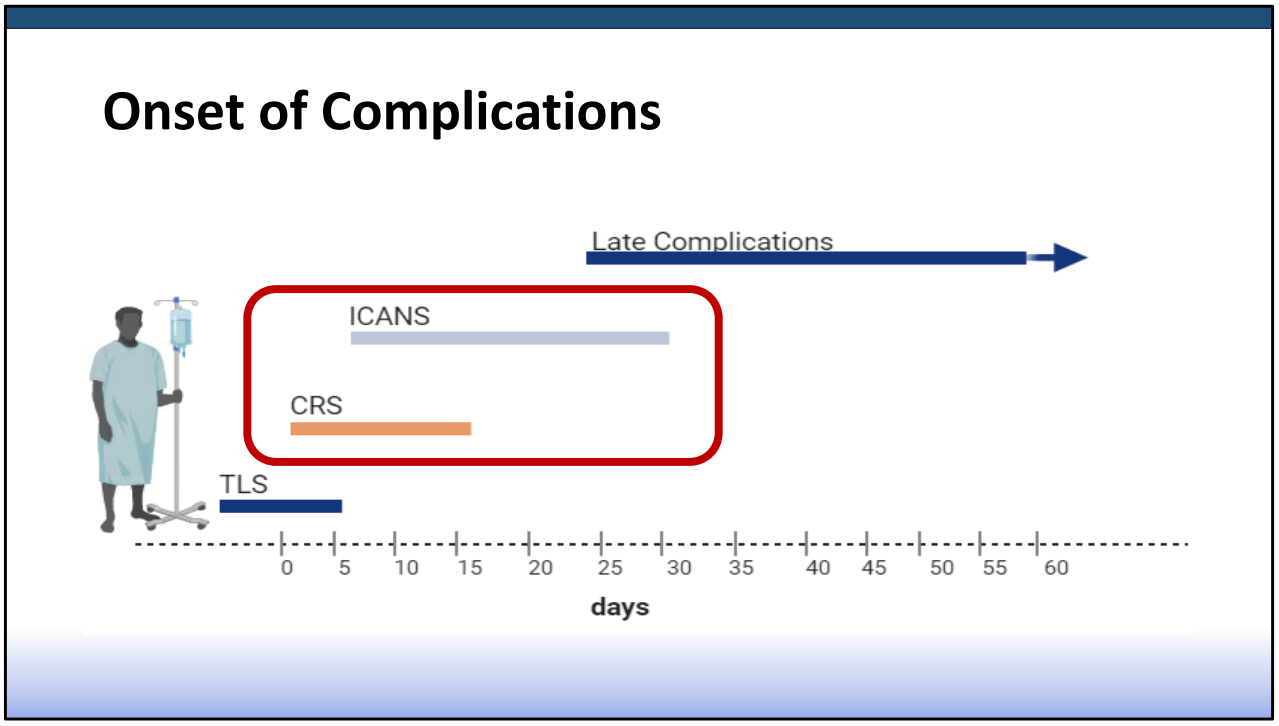
Monica Wattana: When we're talking about the emergency management approach to these novel therapeutics, an emergency in the emergency department never happens at an ideal time when clinics are open; it usually happens at 3 a.m. because that's life. So, to really stress what my colleague Josh said, this podcast and what we're going to talk about will be very helpful, because we'll help you deal with that patient at 3 a.m., when the oncologist may be hard to reach, when the emergency department may be very busy and you have to manage multiple things at once.

The first thing I want you to think about as an emergency physician is the history of present illness. What's bringing this patient to the Emergency Department? When did these symptoms start? Because in general, in the emergency medicine, we don't want to hear about something that happened a month ago, or six months ago, because it probably doesn't have much to do with why they're here right now.

But you do need to extend that time course and I'm going to invite my colleagues to tell you why this is important when it comes to complications of these novel therapeutics. Josh, can you talk about CAR T-cell therapies first?

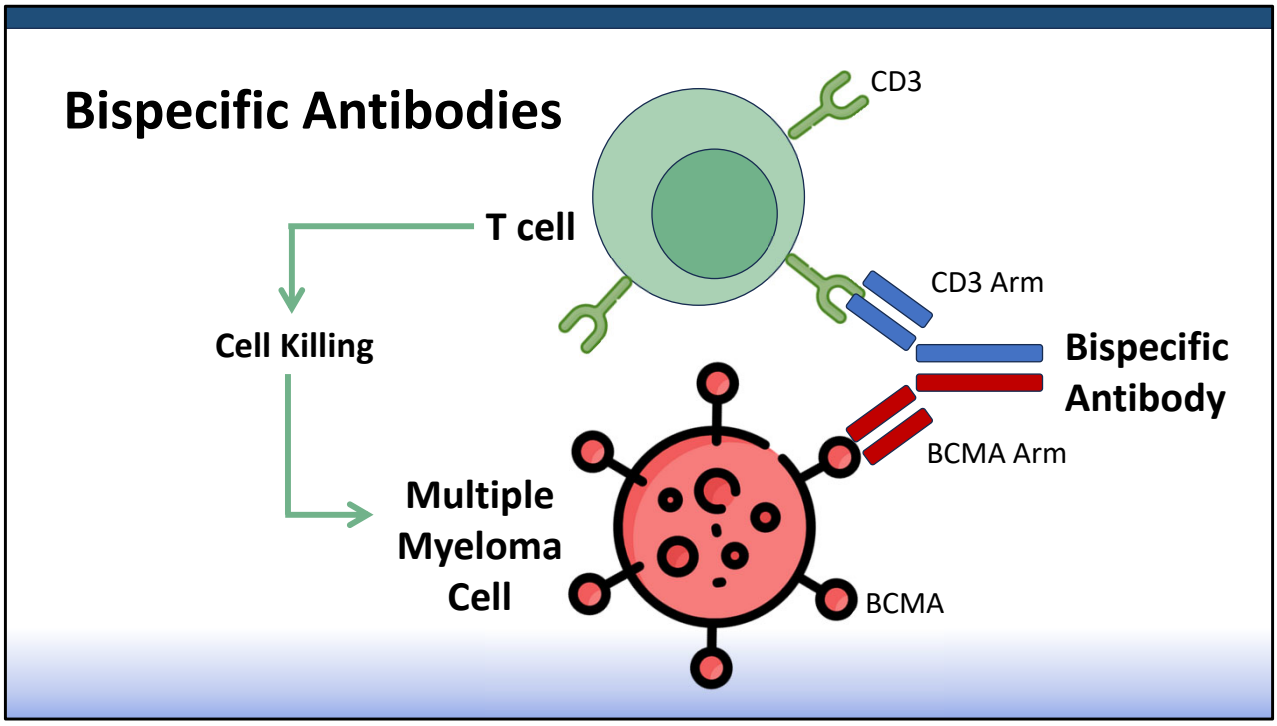


Joshua Richter: Sure. For those of you who may be a little bit less familiar with this are, CAR T is an acronym standing for Chimeric Antigen Receptor T-cell therapy. And in this process, we apherese or collect the patient's T cells, we engineer them ex vivo to attack the cancer, and then re-infuse them into a patient's system in order to fight off their malignancy, in this case multiple myeloma.



Joshua Richter: Typically this process occurs in the hospital and patients receive their infusion of engineered T-cells and then remain hospitalized for approximately the next 14 days. It's during this time period where we see the majority of the acute immune-related events, such as CRS and ICANs. We have certainly noticed that patients can have these delayed toxicities and may subsequently present to the Emergency Department with them. However, the majority of people who are going to have ramifications of CAR T after discharge are going to be infectious in nature.

Monica Wattana: That's super-helpful. Larysa, can you give us some information about bispecific antibodies? When can we expect these symptoms?

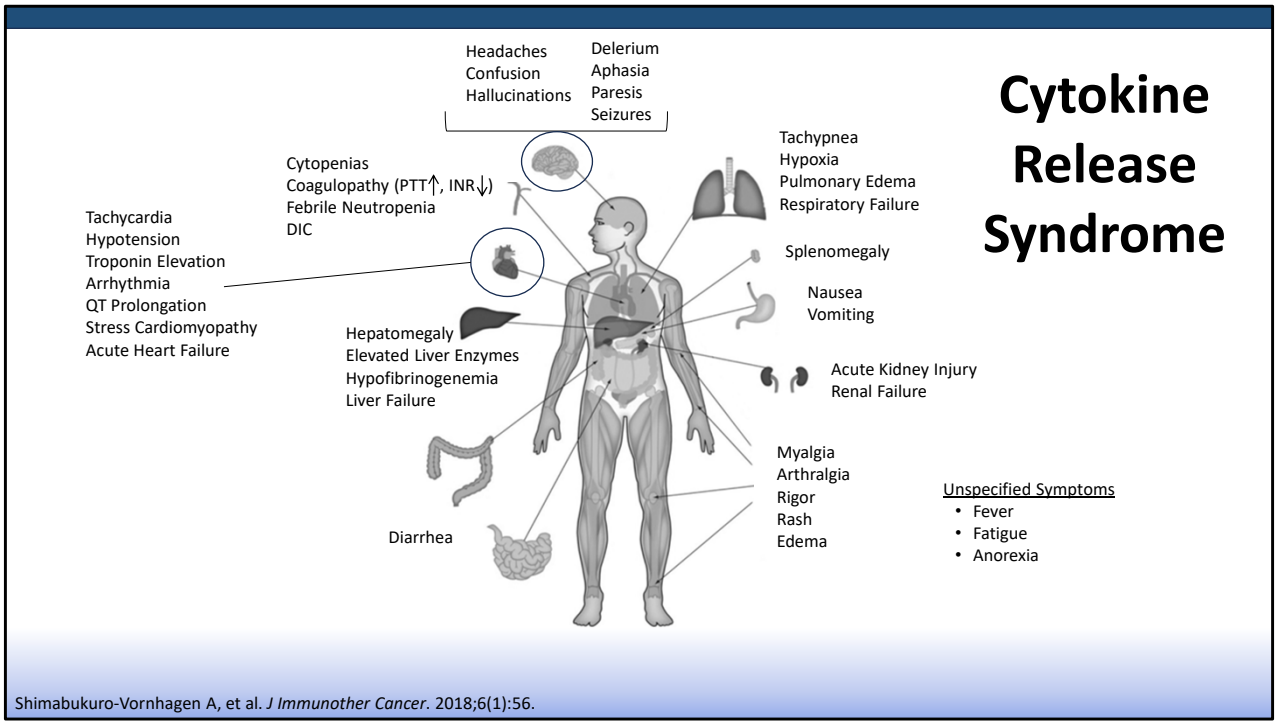


Larysa Sanchez: Sure. CAR T-cell therapies are a little different than bispecific antibodies, as a bispecific antibody is a hybrid molecule that will bind to both the cancer cell and the patient's endogenous T-cells. They're different from CAR T-cell therapies in that we don't engineer them; they're off-the-shelf.

The dosing strategy is also different than it is for CAR T, in that when we dose patients, we admit them to the hospital for initial step-up dosing, and it's during this time that we often tend to see the most CRS events. However, patients are often discharged shortly after the CRS resolves and then they come back to the clinic to continue with full doses of these medications, which are usually on a weekly or bi-weekly basis.

It is still possible, though, for CRS events to happen, even within the first cycle, so this is something that we need to think about. There are slightly different risk profiles for different bispecifics, but as Josh mentioned, infection is also important and is another important consideration for patients who receive bispecific treatments.

Monica Wattana: So, what I'm hearing is that we really need to extend our time course to consider events that happen within a month, which is definitely a change in our mentality, in that we have a higher index of suspicion for these concerns.



Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.

Monica Wattana: I also have a question of how frequently will I, as an emergency medicine physician, see these severities in the emergency department for CAR T?

Joshua Richter: This is a complicated scenario because, literally, as we're filming this podcast, the FDA has moved one of the CAR T assets to earlier line therapy, and we expect an additional approval any time now, meaning that there are an increasing number of patients in the United States who will be receiving these therapies. At the moment, they're mostly given in academic centers, and patients can frequently receive the CAR T-cell therapy and then return to their primary oncologic providers. And subsequently, they may then get admitted to the Emergency Department with some of these delayed reactions. So, the short answer is, bispecifics are becoming more available, CAR Ts are becoming more available, and this is something I think our Emergency Departments need to prepare for.

Monica Wattana: What you're saying, Josh, is that this going to be happening more often; and community physicians and community emergency departments have different resources to deal with these patients. If we're going to be seeing this more frequently overall, this is definitely something to consider.

Larysa Sanchez: It's a great point you've raised, Josh: when bispecifics were coming out, initial dosing was in the hospital. Now we're starting to think about outpatient dosing for even step-up, with the caveat that yes, we want patients to be near our academic centers when we're starting step-up dosing in case a CRS event happens. But it is possible that they may go into a more community setting if they were an hour away, because that was the closest center. This is really something that's going to be coming to the forefront for our emergency room docs.

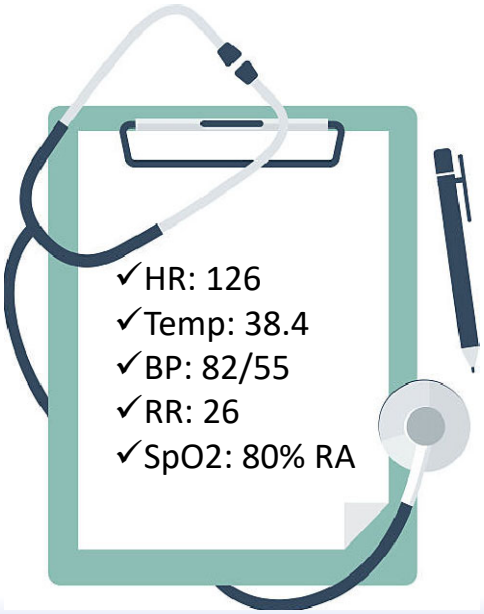
Monica Wattana: Larysa, can you give me more insight into what symptoms, as an emergency medicine doctor, I should be considering when I'm thinking about cytokine release syndrome, which is one of the main side effects for both CAR Ts and bispecifics?

Larysa Sanchez: Sure. A lot of this information was reviewed in the accredited activity, but when we're thinking about CRS in general, what is driving really this is a systemic response to activated T-cells. The drivers here are cytokines, typically IL-6 and IL-1, which are basically causing the systemic inflammatory response that affect any organ in the body.

As you might expect in any systemic inflammation, the most common thing that we'll see is fever, typically at the mild end of the spectrum. Fever can often be accompanied by headaches, myalgias and sometimes exacerbation of pain. When we're thinking about this on a systemic basis, there could also be end-organ dysfunctions such as transaminitis. It's very important to think about CRS as a systemic inflammatory response, and we need to be mindful that it can affect any organ system, especially the neurologic system, which we will talk about later.

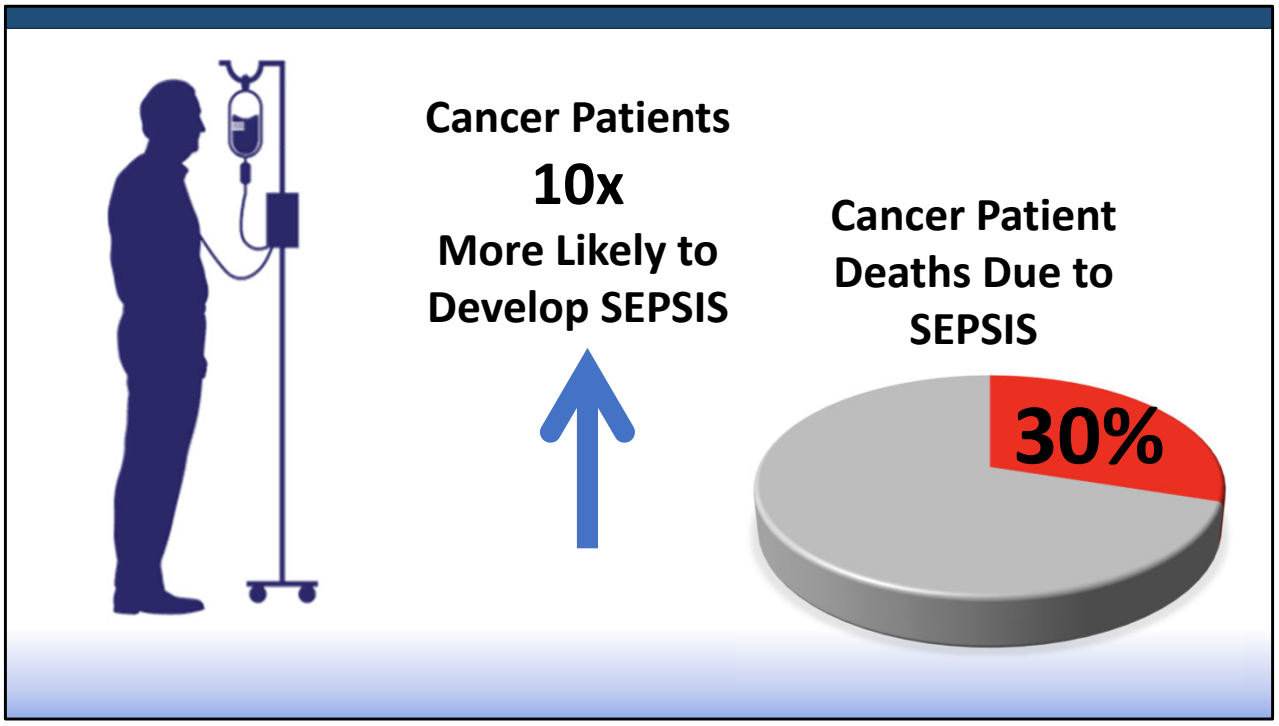
Case Study: Patient in Resuscitation Room 1

- Heart rate: 126
- Temperature: 38.4
- Blood pressure: 82 systolic / 55 diastolic
- Respiration rate: 26
- SpO2: 80% on room air



Monica Wattana: Basically what you're saying is that any system is fair game, and any chief complaint is possible. As an emergency medicine-trained physician, that's our bread and butter. But there are things that we can do to help our oncologists, since this is really a diagnosis of exclusion and how these patients present. Think of it as a big sliding scale, from really subtle to really, really severe, so having a high index of suspicion at all times for any possible system is key, which can sometimes be hard.

We'll give you a sample case that might be helpful to see how having a high index of suspicion is important while you're doing what you do best – treating sick patients. In this case, you have a patient who is brought to one of your resuscitation rooms because they're sick; really, really sick, meaning their heart rate's high, they're tachycardic at 126. They're febrile, their temp is 38.4 and they're hypotensive. For their blood pressure, systolic is 82, diastolic 55. They're breathing a little fast, they're respiratory rate is about 26, and then they're saturating low on room air, 80% on room air.



Monica Wattana: When you have someone that is febrile, hypotensive, tachycardic, there's a big differential that, as emergency medicine physicians, we're trained to think about and we're trained to work up. And the first thing I want to tell you is, do that; do what we do best. When I think of this patient, I'm thinking of sepsis, maybe from a pneumonia source; depending on the physical exam, I potentially think about heart failure or other pulmonary etiologies that require workup with pulmonary imaging to see why the patient's hypoxic, why they're tachycardic. In conjunction with doing a workup to rule out those broad differential diagnoses of severe symptoms such as pulmonary embolism, sepsis and we're treating for those things, I really want to recommend that everybody treat for sepsis.

If a patient is febrile and hypotensive, treat for sepsis, but if they’re on a novel therapeutic, I'd like to ask my oncologist colleagues to give me some advice in terms of labs or other imaging that you’d like, to help make this diagnosis of exclusion. In the emergency department, when all of these things are happening at once, we’re usually not going to be making this diagnosis.

Joshua Richter: I can jump in here. One of the things that you bring up, which is fair, is that what you see is what you get. We can talk about labs that we'd want in this patient who's presenting and the ones we'd want instantly in an ideal setting as if it were a presentation on a board exam. I'd love to have labs like a lactic acid, a procalcitonin, a ferritin and a CRP. But we all know that if this patient is presenting in the middle of the night, we may not have access to those tests and/or the results right away.

One of the things that you brought up, Monica, which is absolutely key here, is to have this as an index of suspicion. If this patient comes in and on their chart or based on a report from a family member who's with them is that they're receiving a therapy like a bispecific or a CAR T, this is where, to use the expression, I shoot first and ask questions later and I would strongly consider adding a dose of dexamethasone in this case. To me, this is similar to how we've seen COPD exacerbations treated, where sometimes we give the antibiotics and the steroids to calm down the inflammation, knowing that high doses and extended periods of steroids may hamper the immune system; but I think one dose is probably warranted if there's any clinical suspicion for CRS.

Clinical Case 1 - CRS IN THE ED

Levels	13-04-2020	13/14-04-2020	15-04-2020	16-04-2020	17-04-2020	20-04-2020
CRP	0.25 mg/dL	9.68 mg/dL				
Ferritin	Normal	941 ng/mL				
D-dimer	0.4 mcg/mL	7.8 mcg/mL				
pro-BNP	Normal	352.50 pg/mL				
Troponin	ND	Normal				
Leucocytes	7.54 x 10^9/L	3.50 x 10^9/L				
Lymphocytes	2.16 x 10^9/L	0.47 x 10^9/L				

Tec 1st step-up dose with premed

Fever 38.2ºC at 16:34 with hypotension at 18:57 and O2 sat 88% at 17:59

Thoracic pain

Cultures of blood, urine, feces, sputum

X-ray

Broad-spectrum Abs → piperaciline-tazobactam

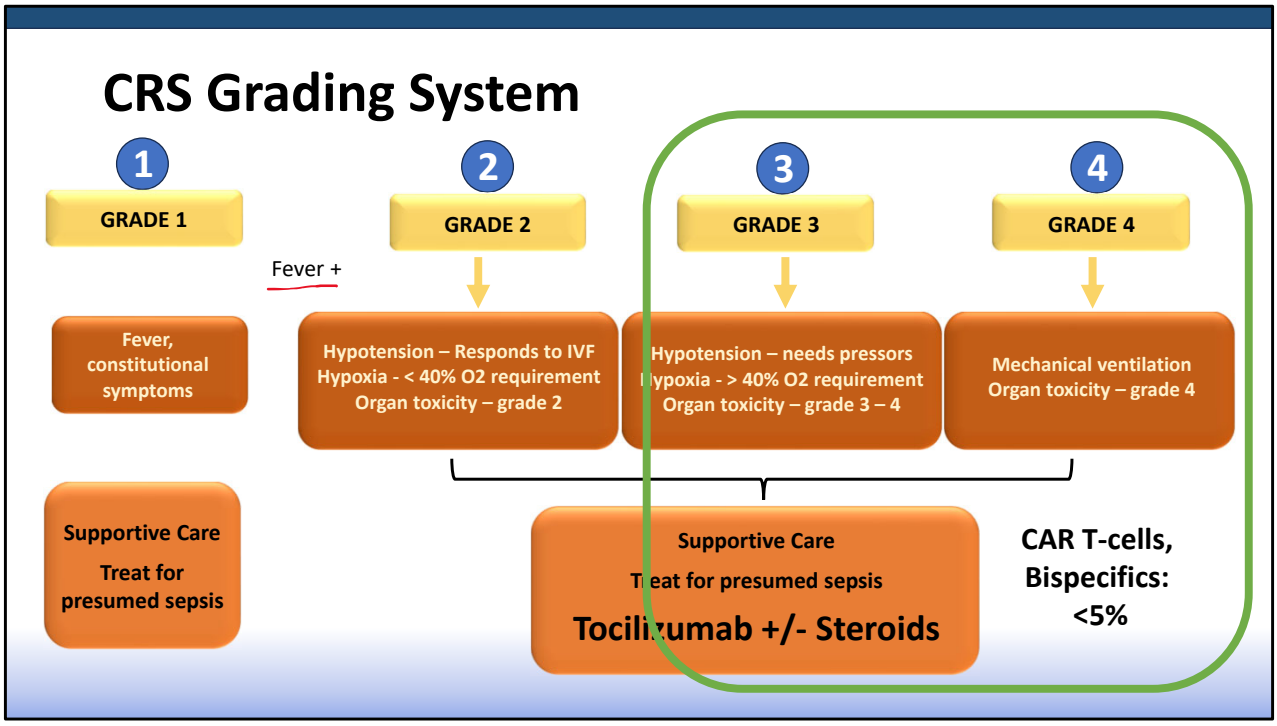
G2 CRS: Tocilizumab on 13-04 20

Cardiological evaluation: Normal

O2 sat = oxygen saturation.

Monica Wattana: That's very helpful. In our institutions, many of us have standard ordering panels, so, I'm glad that Josh brought up the fact that there are tests that we don't often order, such as the ferritin levels, ESR, CRP; these will be helpful because they are tracked in clinic. If you think that the patient does have CRS, add those labs on along with the procalcitonin and lactic acid.

Now, talk to me about the grading system: how do I know how severe a patient is? Because if they're in my emergency department and are already symptomatic, in my head, they're already severe.



Larysa Sanchez: I'm happy to take this. When we look at the CRS grade, it ranges from grade one to four; and usually grade one has mild fever, constitutional symptoms. They're just generally feeling unwell.

But when we start getting into the higher grades, we start seeing more end organ dysfunction. So, grade two, generally, is hypotension, which is responsive to fluids; and hypoxia, which requires basically nasal cannula to help to improve. At this point, when we go through the grading, it now depends on blood pressure status and oxygenation status.

Grade three is hypotension that's refractory to IV fluids, requiring pressors, and hypoxia that may require a greater level of support, moving away from nasal cannula to potentially like non-rebreather, etc. Grade four is mechanical ventilation requiring more pressor support and possibly transfer to the ICU.

Monica Wattana: I want to press on my colleagues who are listening to this podcast, if a patient is visiting you in the Emergency Department, most likely they're already grade two or higher; they're not going to be presenting at 3 a.m. for something that is asymptomatic. You need to be already thinking about treatment and if, as Larysa just said, the patient may need to be transferred to higher level care, if you're in an institution or in urgent care that doesn't have capability for the treatment of these patients.

Monica Wattana: Just so that my colleagues who are viewing this can have a better understanding, because CAR T and bispecifics are different, how frequently can I expect a patient to be presenting in grade three or grade four for bispecifics versus CAR-T?

Larysa Sanchez: Based on clinical trial data, most CRS events are grade one or two, for both CAR T and bispecifics. CAR T therapies are associated with slightly higher rates of CRS overall compared to bispecifics, ranging from 70 to 90%; whereas with bispecifics, up to 70% of patients will develop some type of CRS. For both bispecifics and CAR T, grade three or four are much less common; generally less than 5% should be seen.

Joshua Richter: Layrsa did a phenomenal job of going through the one, two, three, and four grading system; and we all know that, once a patient is in the ER, if the patient is requiring pressor support or mechanical ventilation, that's an automatic ticket to the intensive care unit. One of the things that the three of us have all done at our centers, and I would encourage other centers who are going into the field of giving these type of drugs, is to have good conversations between the Emergency Department, Oncology Department, and the ICU to consider transfer to ICU for someone with CRS, even sometimes with a grade two CRS; because if they're starting to worsen, these patients can turn quite quickly. So, even though the typical requirements of pressor support and mechanical ventilation are the barrier the patient needs to reach, we have agreements from our ICU about these specific situations. So, if we see a patient that we're concerned about, because they may be on their second liter of fluid and we feel that they're heading in a worsening direction even though they haven't reached the usual thresholds, they might accept the patient sooner, to prevent us having an urgent transfer to the ICU.

Monica Wattana: That's so helpful. From an emergency medicine perspective, depending on where you work, if you're already seeing grade two, you might consider transfer to a higher level of care facility, even when the patient's vital signs are within normal limits and their grading scale number is not that high. I's definitely something to consider. Larysa, in terms of grades versus treatments, what's the recommended standard?

NCCN Guidelines: CRS Treatment Based on Grade

CRS Grade	Anti-IL-6 Therapy	Corticosteroids[j,k,l]	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (>3 days)[h] in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)[i,t]	For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS (<72 hours after infusion)	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[q] • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[r] requiring low-flow nasal cannula[g] or blow-by	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose).[j] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total[t]	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider dexamethasone 10 mg IV every 12-24 hours depending on product[m,n]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[g] face mask, nonrebreather mask, or Venturi mask.	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours.[m] If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation).	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours.[m] If refractory, consider 3 doses of methylprednisolone 1000 mg/day IV; if refractory, consider dosing every 12 hours[o,p]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

Larysa Sanchez: As I mentioned before, when thinking about the pathophysiology, CRS is really driven by IL-6. That's the mainstay of therapy, with the goal of reversing the inflammatory event that happens in CRS.

At least in academic centers, at the first onset of very mild CRS fever, we give usually tocilizumab, which is anti-IL-6 therapy, to decrease the inflammatory response and allow us to get through the step-up dosing; this is really the backbone of treatments for CRS.

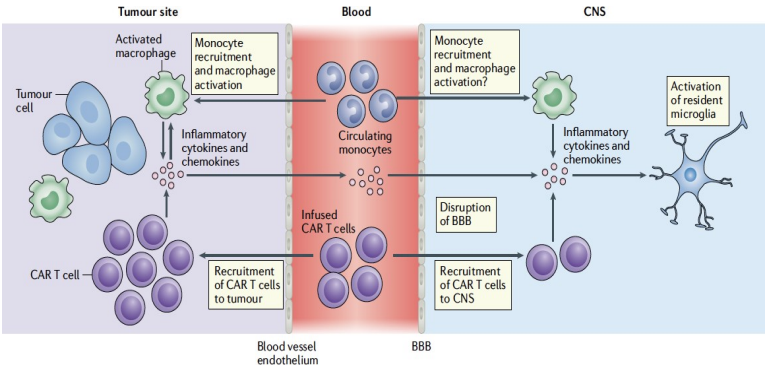
Grade one can sometimes be monitored if it's prolonged, then if the CRS is not improved with anti-IL-6 therapy, treatment moves on to corticosteroids such as dexamethasone, to continue to try and decrease the inflammatory response. If a patient has grade two from the onset, they're absolutely someone who should get tocilizumab to start, with potentially DEX if the CRS doesn't resolve in a timely fashion. Those are really the two main agents that we have.

Monica Wattana: Because many institutions, even other academic centers, may not have access to tocilizumab, we need to think about transferring the patient or, as Larysa said, giving a first dose of high-dose steroids. If you're somewhere that doesn't have to tocilizumab, that will be really, really key.

Joshua Richter: Just to add to this discussion, there is an alternative called siltuximab, which is another anti-IL-6; because when these patients come in, another key partner is our pharmacy colleagues concerning the specific therapeutics we have available. So absolutely, TOCI, as Larysa pointed out, is the way to go. If we don't have that, siltuximab is another option, but every Emergency Department out there has steroids.

Monica Wattana: That we do. Moving on, given that every Emergency Department has steroids, Josh, can you talk about the second side effect, for both myself and my colleagues listening in: what will the emergency medicine physician need to consider with these new novel therapeutics?

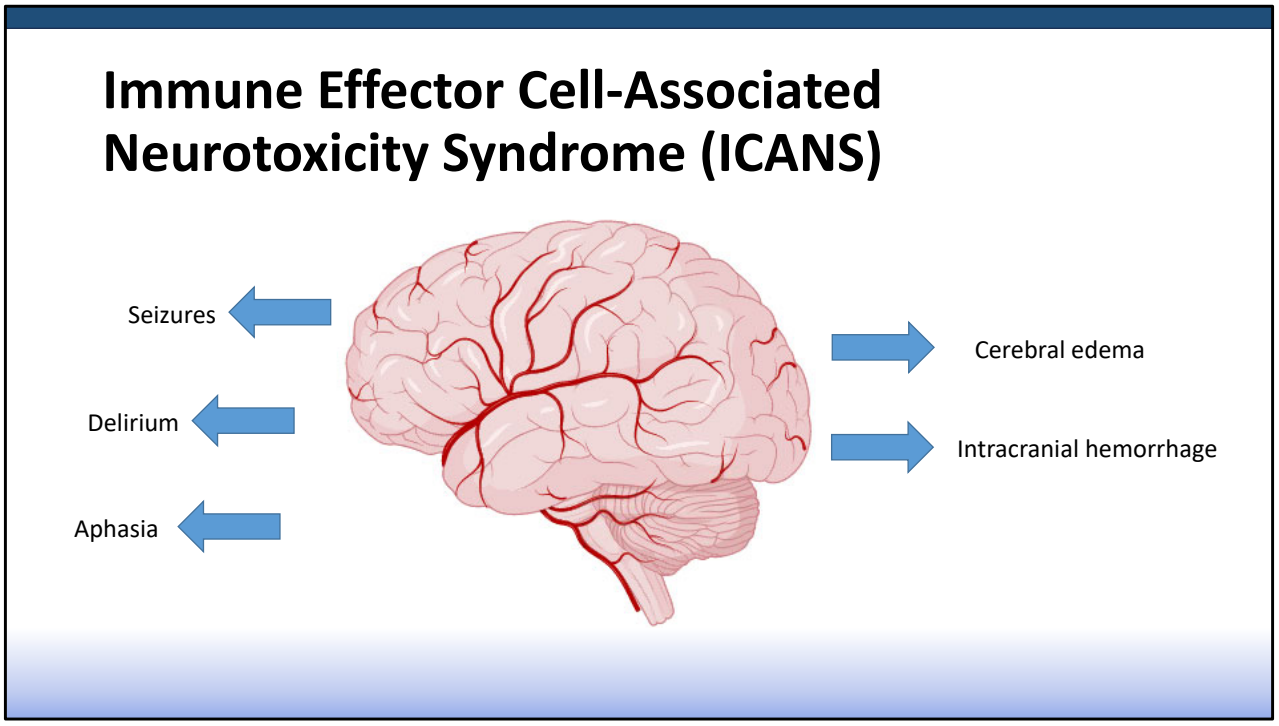
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)



- CAR T-cells have the ability to penetrate the CNS, crossing the blood-brain barrier
- BsAbs-related ICANS is mediated by the cytokynes released by T- lymphocytes, and the T-lymphocyte can potentially penetrate
- This can be related with the fact that after BsAb the incidence and severity are lower

Morris EC, et al. *Nat Rev Immunol*. 2022;22(2):85-96.

Joshua Richter: I think this one is even harder in many ways. This is ICANS, which is Immune Effector Cell-Associated Neurotoxicity Syndrome. ICANS is mediated by exactly what Larysa was talking about: activated T-cells start cranking out cytokines like IL-1, and now those T-cells are going to cross through the blood-brain barrier and start causing neurologic issues.



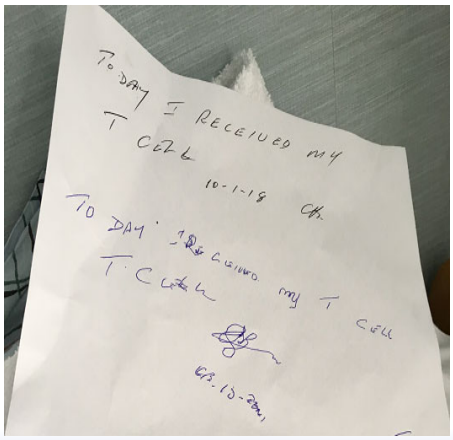
Joshua Richter: This runs a huge gamut, everything from headache, which people may have just from listening to my voice, all the way through seizures, comatose, altered mental status. It can be really, really difficult to tease this out and what's causing it, especially in the early grades. Because we may have a variety of patients who have some baseline neurologic dysfunction, if there's any way to identify their baseline, that may help distinguish ICANS from some other concomitant neurological issues.

Monica Wattana: I see. When you're in the clinics monitoring these patients, what are you doing to determine the patient's baseline? And what can I continue when I'm seeing this patient in the Emergency Department, whether it's in the waiting room, in the not-ideal situation versus in a busy Emergency Department setting?

Joshua Richter: I think the hardest part about seeing these patients in the emergency room, as opposed to our clinic, is that we see these patients over long periods of time. We know their baseline, we know when things are off. When they come into the emergency room, it's hard to have a frame of reference. Ideally, the patient has a family member with them or there's a family member to call to say, "I'm here with your uncle. He's a little confused. Is this new for him? When did this start?" I think that context really helps.

ICANS Grading Includes the Immune Effector Cell-Associated Encephalopathy (ICE) Score

Points	Assessment
4	Orientation: year, month, city, and hospital
3	Naming: ability to name 3 objects correctly
1	Following simple commands: ex, close your eyes and smile
1	Writing: able to write a standard sentence
1	Attention: ability to count backwards from 100 by 10



Joshua Richter: What we use in the clinic is something called the ICE score. The ICE score is a 10-point scoring system that evaluates things like orientation, naming and, most specifically, handwriting. It turns out that things like micrographia and dysgraphia can be some of the earlier telltale signs of ICANS. When we have patients who are receiving initial therapy with CAR Ts or bispecifics, we have them write a daily sentence. So, you could always have the patient write a sentence while they're waiting to be evaluated; and if things are all over the place, that might be a sign that this is ICAN.

Monica Wattana: To my colleagues out there: basically, when we're evaluating a patient who's on bispecifics especially, everything is subtle. The patient may say their chief complaint is that they're just not feeling well, maybe they feel a little off balance. That is how they're going to present. And I don't know about any of you, but before these treatments came out, I never got a sample of anybody's handwriting in a busy waiting room, nor do I have a piece of paper. That's why I really want to tell you this, and to make sure that all of our colleagues on board that this is actually very important.

So, out that pen. It's hiding somewhere since most of us are on electronic medical records now; and actually ask what sentence they usually write in clinic. An easy way to help facilitate this, if you're able to contact the oncologist, you can take a screenshot of the handwriting sample and either put it in their electronic medical record or text it to them, because they'll know what the patient's handwriting looked like and if it's changed. And these changes are that subtle. It's really difficult to evaluate when the patient's in a waiting room.

NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Grading

Neurotoxity Domain[r]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[s]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[t]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[u]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

Monica Wattana: Josh mentioned the ICE score. The ICE score is really, really important, but you don't have to memorize it; there are calculators that are available now [an example of an ICE Calculator is Cancer Calc, Clinical Tools for Oncology Professionals, available at: https://cancercalc.com/ICANS_grade.php]. You just need to remember that there is a score and it should be included when you have a high index of suspicion that a patient might be having ICANS.

So, Josh, tell me more about the grading of ICANS.

Joshua Richter: Just as Larysa described for CRS, grading for ICANS is on a scale from grade one to grade four with gradual worsening, and it's really tied into that ICE score. So, if you have all 10 out of 10 points, you don't have ICANS, but a score of seven to nine is grade one; three to six is grade two and zero to two is grade three. And if your patient is, literally, completely unarousable and not able to answer the questions, that's grade four.

In terms of how we approach treating ICANS and what symptoms ICANS is associated with, grade one ICANS can be very, very subtle, can even be things as simple as a headache. And how many patients in an ER right now have a headache? It's really hard to tell. Often for grade one, we don't start any treatment; it's really when we have an index of suspicion for grade two or higher ICANS that we start intervening.

NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Grading

Neurotoxity Domain[r]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[s]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[t]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[u]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

Monica Wattana: That's really helpful for us, because many patients who are treated with bispecifics will present with subtle chief complaints. I just want to get a good sense of how many of these patients we might see in the Emergency Department: in your own patient population, how many of your patients have you sent to the Emergency Department? How severe are they, usually? How many severe grade three/fours have you sent versus grade ones?

Joshua Richter: One of the things that we're seeing is a rise in more severe cases. As Larysa described with CRS, the general rates of grade 3, 4 ICANS are very low and we're talking about single digits in the CAR T's or the bispecifics. The reality, however, is that these therapies are moving from clinical trials to standard of care in academic centers to standard of care in community centers. On a clinical trial, you have to fit all of the inclusion and exclusion criteria; but you can treat a sicker or more advanced or more aggressive cancer patient with these therapies in standard of care. And now we're starting to see anecdotally a higher incidence [of adverse events] when we're giving these therapies [outside of a clinical trial]. So, we've sent a couple of grade 3/4s within the last few months to our ER, and it was very scary.

Monica Wattana: To my colleagues, the biggest thing is, with just our basic emergency medicine training, you're very well equipped to work these patients up in the Emergency Department and to treat the worst of the worst patients. As Josh said initially, they can be presenting with like status epilepticus or with vasogenic edema; those things we know how to manage.

NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Treatment

Treatment by Grade	No Concurrent CRS[x]	Additional Therapy if Concurrent CRS
Grade 1[v]	• Supportive care	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[aa, †]
Grade 2	• Supportive care • 1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12 hours, if no improvement.	Anti-IL-6 therapy as per Grade 1[aa] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[w]	• ICU care is recommended • Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours[k,y] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.	Anti-IL-6 therapy as per Grade 1[aa]
Grade 4[w]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[k,z] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per Grade 1[aa]

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Monica Wattana: It's more of the subtle findings, to make sure that you have a high index of suspicion and that you work the patients up as if you were working up a patient who might potentially be getting worse and might present with status. Because many times, if a patient has just a low-grade headache, if I didn't ask the right questions, I might not get that CT scan. And when you're working these patients up in the Emergency Department, the grading for ICANS involves imaging: even though the imaging might be negative, it's part of the diagnosis and it's useful to get to rule out other diagnoses, which as an emergency medicine physician, is our job: ruling out other worst-case scenarios, so that the oncologist can drill down and treat ICANS, if that's it.

Let's talk more about this grading system, because, especially with subtlety in symptoms and work ups, as an emergency medicine physician, I need to know, when do you want to be called? Do you want to be called with every person that has a headache? Because if you want, I can, but it might be pretty bothersome to you, as well. In terms of communication, what would you prefer?

Joshua Richter: At the current time, the surrogate for us is that we're administering most of these [novel immunotherapies] on the inpatient side during the initial dosing; but exactly as Larysa described, it's moving to the outpatient setting. What this means is that right now, when the majority of these [adverse] events happen, a nurse practitioner, a PA, or a physician gives us a call in the middle of the night, with the information that the inpatient is developing these symptoms. Early intervention is important, so I would prefer a call earlier on rather than later, and consider ICE one of

the vital signs. So, when our NPs call us at two o'clock in the morning that Mr. Smith is having some event, they'll say, Mr. Smith, here are his vital signs. His O2 sat, here's his blood pressure, temperature, all of that. ICE is 10 out of 10. It's part of that initial assessment, whether or not it's CRS or ICANS. Anytime there's any immune-related adverse event, it's part of the vital signs, and it's better to call us early on than later.

Monica Wattana: That's really helpful. With these new therapeutics, it's important to impress on everyone who's tuning in to this podcast, we play a vital role. It's not a role where the emergency medicine physician is operating in an isolated silo anymore. Since these patients are being monitored frequently, we're integral in their care. Letting the treating team know earlier, even if it's at night, about any concerns that we might have actually is helpful; and as Josh just said, it's actually welcome. So, I definitely agree, give your patient's oncologist a call, if you even suspect that they might be having a side effect from their treatments.

Josh, when we're talking about these treatments for the different grades, can you just go over what I should be thinking about for ICANS in these patients and what should I initiate within the emergency department?

Joshua Richter: Sure; so, the first pass we think about, obviously, is the grade of the ICANS; but then the second pass is, what is the relationship to CRS? Because you can have CRS without ICANS, ICANS without CRS, or both together. Commonly, when you have ICANS, it's occurring with or just after CRS. Not always, but most of the time, that's the way it happens. The reason this has an impact is because, as Larysa pointed out, drugs like tocilizumab are going to be our first-line approach for the majority of CRS. TOCI does not cross the blood-brain barrier, so, if you're having ICANS without CRS, there is actually no role for tocilizumab.

However, if you have a patient who's having CRS and ICANS, as a first pass, you're still going to give something like tocilizumab. But in general, once we get beyond that, or if you don't have concomitant CRS, dexamethasone is going to be our first pass.

So, dexamethasone, 10 milligrams, IV times one. You can continue that up to Q6 hours. If that doesn't work, as the grade of ICANS goes up to grade two or grade three, we often start considering the addition of anakinra, also known as Kinneret, the anti-IL-1 therapy. Dosages ranging from around one to 200 milligrams, sub-Q, Q8 hours.

As a next step, you can escalate the steroids to high dose methylprednisolone, up to a gram QD to BID, up to three days. But as we're getting up to these higher levels, you really need to start thinking about neuroimaging, transfer evaluation by the ICU, and anti-epileptic therapy, even if there's no evidence of the patient seizing at that time, because this can progress to status epilepticus. That's the pathway we generally follow.

When a Patient Presents to the ED with Symptoms of Possible CRS, ICANS

- History concerning timing of MM treatment is key
- Early recognition of CRS, ICANS and appropriate treatment required to improve outcomes, decrease morbidity
- Symptoms of CRS, ICANS can be subtle: high index of suspicion needed
- If tocilizumab or higher level of care not available, consider early transfer of patient, consult with patient's oncologist

Monica Wattana: That's really helpful. If I'm considering transferring a patient out of my institution for higher level of care, you do recommend starting anti-epileptic therapy. Is that correct?

Joshua Richter: Yes; many years ago, when I started practicing, it was all Dilantin. But I think now Keppra seems to be one of the main drugs of choice, to load a patient where you have concern for progression of status epilepticus. I think risk-benefit is there. There's no problem starting the anti-epileptic therapy and discontinuing it later on, because these patients may require transfer, and nothing would be worse than having a patient go into status during the hospital-to-hospital ambulance transfer. So again, when in doubt, I think pushing a little bit harder here with the protective therapy is a good idea.

Monica Wattana: That's really, really helpful.

Joshua Richter: We've talked about any great points concerning how to manage these patients. But with all of this, let's try to boil it down to the bare essentials of what you need to walk away with. So, Larysa, you're getting a call in the middle of the night from our ER colleagues. What do you want them to know about a patient where you have a concern for CRS or ICANS?

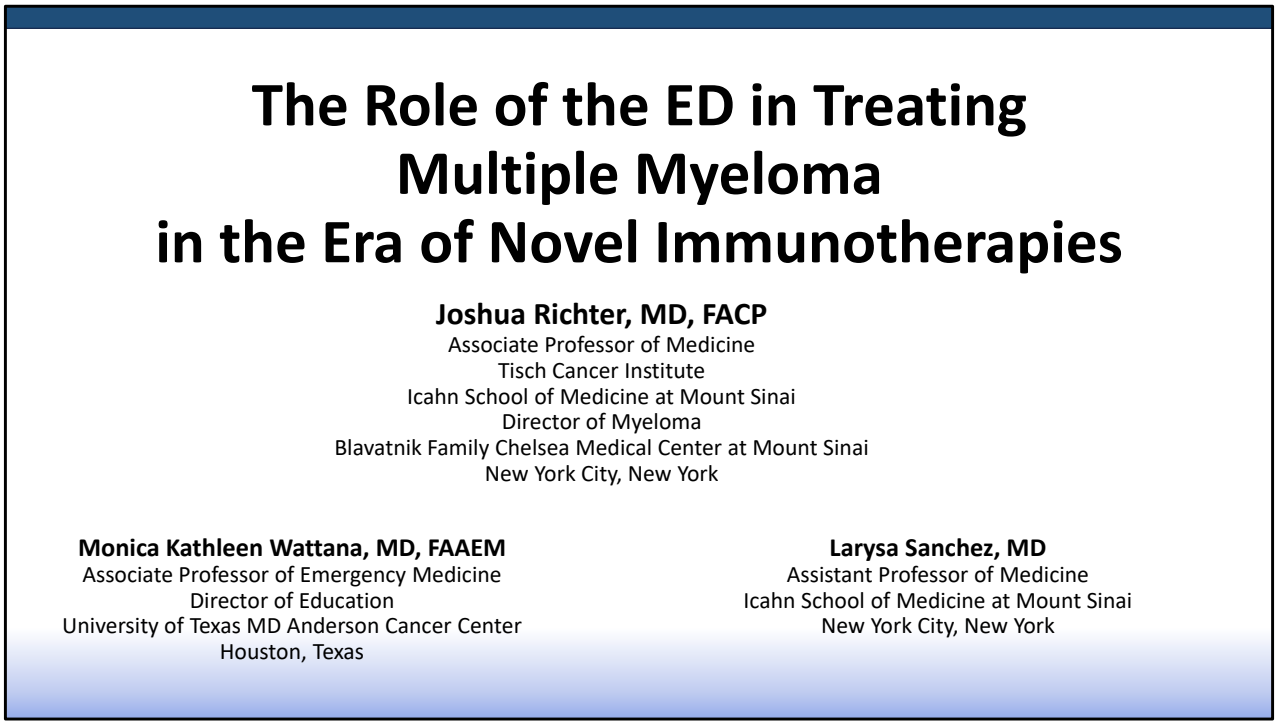
Larysa Sanchez: For our emergency room colleagues, history is key. When did this patient receive this most recent treatment that they were on? That's going to be the key data point that we need as oncologists to help guide us in whether this is going to be infection or CRS or whatever else there may be on the differential.

And I've made this analogy before, timing and intervention is extremely important. So, similar to our "Stop Sepsis" campaign, I think "Stop CRS" is key. When we recognize CRS early, we can intervene early with the appropriate medications to improve patient outcome and decrease morbidity. I think that's the key point here, history taking and early intervention.

Joshua Richter: Monica, I think one of the points you bring up that's most critical, is that the Emergency Department is not siloed. They're a critical part of the care team. What are the final bullet points you'd want to impart to your emergency room colleagues?

Monica Wattana: The most important thing is that I want to instill confidence in all of you: our training is excellent and wherever you've been trained as an emergency medicine physician, you're able to handle these complications, even the biggest, broadest range of spectrum for CRS or ICANS. I want to press on the index of suspicion, because so much of this is subtle and it's easy to miss. Even the smartest person can miss things when a so many things are going on at once. So, having a high index of suspicion and asking the right questions will be really, really key for us to nail the diagnosis, or to help our colleagues to nail the diagnosis once the patient is admitted.

The second thing is, we all practice in different environments. If you're somewhere that doesn't have tocilizumab or higher level of care, transfer early or call the patient's oncologists, if they're available, to consider initiating transfer for higher level of care, so that these patients do not get worse sooner.



Joshua Richter: This has been an absolutely wonderful podcast, really the archetype for the way modern medicine ought to behave, which is complete collaboration across subspecialties including emergency medicine, oncology, along with our pharmacy colleagues, our ICU colleagues, neuro colleagues; it takes a village. With that, I'd like to thank the viewing audience for listening to this podcast. If you haven't had a chance yet to view our companion accredited activity yet, please check it out in the link below for a complete picture of potential treatment-related adverse events associated with some of these novel immunotherapies for multiple myeloma and how these patients might present to the Emergency Department.