THE PATH FORWARD FOR CAR-T

This interview was conducted on May 14, 2021 with Dr. Shen and Dr. Frigault to discuss the issues and challenges in expanding the use of break-through CAR-T therapies.

Dr. Angela Shen, MD, MBA

Dr. Angela Shen has been developing oncology and hematology investigational products including small molecules, biologics, and cell/gene therapies for the past 15+ years. She has unique, deep knowledge of the cell and gene therapy landscape, having been on the Novartis deal team that licensed U Penn's CAR-T platform in 2012, and subsequently built and led industry's first clinical team to design and launch a multi-site, registrational CAR-T trial, which resulted in the first approval for Kymriah® (CTL019; CART-19) in August 2017. Since then, she has contributed to the development of multiple other novel cell therapy assets. Dr. Shen has designed and executed dozens of Phase I, II and III clinical trials, including first-in human and registrational trials, and prior to her work in cell and gene therapy, made key contributions to the development of approved agents including Cotellic® (cobimetinib; MEKi), Farydak® (panobinostat; HDACi), and Adakveo® (crizanlizumab; anti-P-selectin).

Dr. Matthew Frigault, MD

Dr. Matthew Frigault is an oncologist working within the Department of Hematologic Malignancies at the Massachusetts General Hospital Cancer Center and as an Instructor at Harvard Medical School. Dr. Frigault's current clinical activities include attending on the inpatient bone marrow transplant and cell therapy services, managing outpatient cellular therapy patients and overseeing the cellular therapy infrastructure responsible for MGH's standard of care and clinical research efforts. His current research is focused on the translational aspects of cellular therapies with the goal of developing the next generation of cellular therapies. He is PI of multiple first-in-human studies targeting hematologic and solid malignancies focused on optimizing current cellular therapy approaches through CRISPR gene editing, novel immunomodulatory approaches for toxicity management, and in-depth clinical correlatives.

1) What are your overall thoughts on the CAR-T landscape?

Dr. Shen:

I think CAR-T therapies are here to stay and we are still in the early days. The field has managed to show that CAR-T works well in certain patient populations with relapsed or refractory hematologic malignancies by targeting CD19 and BCMA, but that is just the tip of the iceberg. When CAR-T therapies move into earlier lines of therapy and when they are approved for additional hematologic malignancies as well as solid tumor malignancies – the demand for CAR-T therapies will be massive compared to what it is today.

Dr. Frigault:

Cellular therapy is a rapidly growing field that doesn't show any likelihood of slowing. In 2020 alone we saw a 40% increase in CAR-T infusions (>100 patients in total at our institution) and estimate treating approximately 100-125 patients in 2021 despite an ongoing pandemic and decreased ability for patient travel. We now have five CAR-T approved indications including DLBCL [Juliet, ZUMA-1, TRANSCEND], FL [ZUMA-5], MCL [ZUMA-2], B-ALL [Eliana], MCL [ZUMA-2] and MM [KarMMa]. Looking forward we are seeing additional indications in MM [CARITUDE-1], adult B-ALL [ZUMA-3], and potentially 2nd line large cell lymphoma [Belinda, ZUMA-7, TRANSFORM] in place of autologous stem cell transplant. This is extremely encouraging given the fact that only 15% of relapsed DLBCL patients will be "cured"

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with salvage chemotherapy and 3rd line CAR-T therapy. Even more exciting is the fact that we are seeing potential indications in solid malignancies such as melanoma, H&N, cervical and lung with lifileucel showing a 36.4% ORR and mDOR that had not been reached at a median follow of 28.1 months [C-144-01 cohort 2] in *checkpoint refractory* metastatic melanoma. We are also seeing encouraging data in synovial sarcoma, H&N tumors, esophageal and EGJ cancers [MAGE-A4, MAGE-A10, NY-ESO] suggesting that cellular therapy for solid tumors is in our not-so-distant future. Beyond oncologic indications, we are seeing programs in autoimmune disease, B-cell depletion to reduce allo-sensitization and infectious diseases growing utilizing a wide array of cellular therapy products. As such, programs around the country are continually building out institutional infrastructure to handle the growing patient and prescriber demands with a focus on efficiency, and safely, prescribing these potentially curative therapies.

2) What are your overall thoughts on CAR-T induced toxicity management and what are the unmet needs?

Dr. Shen:

Back in the days before CAR-T therapies were approved, drug developers were concerned by the frequent and severe toxicities that were correlated with CAR-T therapy. In some of the earlier trials, one-third to one-half of the patients were admitted to the ICU, and it wasn't uncommon for patients to need ventilator and/or pressor support. Fortunately, the clinicians at CHOP and U Penn figured out that using tocilizumab could help rescue most patients experiencing out-of-control CAR-T induced toxicities, and since then, the field has learned through collective experience and data that giving tocilizumab and moderate doses of steroids do not have deleterious effects on CAR-T efficacy. That has led to earlier intervention with toci, and overall reduction of rate and severity of toxicities. The more manageable toxicity profiles and favorable risk-benefit ratio enabled approval of multiple CAR-T therapies.

Now that we've had the first wave of CAR-T approvals, the thinking around unmet need now shifts toward accessibility, scaling up, and affordability. A major bottleneck is the intense effort and expenses that are required to carefully observe patients and manage any potential CAR-T induced toxicities. Although the toxicities are

Dr. Frigault:

The management of cellular therapy toxicities, primarily focusing on cytokine release syndrome (CRS) and immune cell associated neurotoxicity syndrome (ICANS – previously called CARTOX or neurotox). Currently our focus is on the management of acute toxicities, typically in the inpatient setting, in patients with symptomatic CRS and ICANS. It has been difficult to compare absolute grades of CRS/ICANS across pivotal studies due to differences in grading systems (ie. Lee 2014 vs Penn vs ASTCT 2019) as well as the growing and evolving management strategies over the past decade. Based on the best available data using real world patient series and aggressive management (including early tocilizumab for grade 1 CRS and prophylactic steroids), we still are observing rates of CRS between 45-80% and ICANS between 18-58% with approx. 36% of patients still requiring tocilizumab and/or steroids.[1] Although these studies report low rates of "high-grade" CRS and ICANS, this is primarily referring to patients requiring ICU level care, not clinically significant hypotension and/or hypoxia that necessitate inpatient hospitalization and urgent intervention. Although grade 2 CRS is classified as "low-grade" it still results in upwards of 1/3 of CAR-T patients receiving toci/

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now more manageable, it is very expensive and time-consuming to care for these patients.

steroids. These distinctions translate into prolonged hospitalizations and increased length of stay (median LOS 15 days)[2] despite FDA only requiring a minimum of 7 days of daily observation. Furthermore, even when utilizing aggressive, up front CRS/ICANS management with outpatient infusions [OUTREACH, PILOT], 54% of patients will require admission for acute management.[3] As in the management of graft-vs-host disease, the holy grail of CRS/ICANS treatment is therefore CRS/ICANS prevention. If a treatment strategy can predictably, and with high confidence, decrease the need for subsequent intervention we will be able to offer these therapies in a broader context to more patients. The fact that despite our efforts 1/3 of patients eventually requiring toci/steroids emphasizes how the current management strategy has yet to be optimally determined.

3) What are current challenges of toxicity management such as pressure points, limitations and constraints?

"Overall, reducing the rates and severity of toxicity will allow us to treat more patients, treat them in the outpatient setting, and decrease treatment related morbidity."

—Dr. Matthew Frigault

Dr. Frigault:

Currently the main pressure points and limitations of toxicity management involve the inability to predict who will develop tox and when it will happen. Although we have median days to onset and rates of tox, we are obligated to treat any and all early toxicity as a potentially life-threatening event. As such, a majority of care remains in the inpatient setting for many products. Additionally, in order to build our outpatient infrastructure, we've had to "prepare for the worst, hope for the best" which includes housing within 2 blocks of our site, daily visits through day +14, early admission for any fever, creation of a hospital "crash-bed" for CAR-T patients and development of a dedicated cellular therapy service. A major limitation is our inability to hold beds for CAR-T patients, therefore if a substantial number (upwards of 50% as above) require admission and the majority who are admitted then need intervention, we will eventually hit a bottleneck. The acuity of these patients also mandates that beds be made available immediately, a growing problem as we typically run at near capacity due to COVID and standard operations. From a financial standpoint, with increased toxicity, single patient outliers can dramatically impact overall reimbursement with long term ICU utilization and subsequent need for facility placement. Overall, reducing the rates AND severity of toxicity will allow us to treat more patients, treat them in the outpatient setting, and decrease treatment related morbidity.

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4) How has our understanding of Mechanism of Action (MOA) for CAR-T induced toxicity (CRS, ICANS, HLH/MAS) evolved?

Dr. Frigault:

Neither CRS nor ICANS were predicted with the early studies of CAR-T in NOD–SCID–γ chain receptor–knockout (NSG) mouse models. This is largely due to the fact that this model lacks an intact innate immune system that is the primary driver of CRS. Based on our current understand, CRS is a clinical syndrome mediated by antigen-specific T cell activation and expansion, with strong interactions with innate immune compartments mediated by the IL-6 signaling pathway. Interestingly, CRS is remarkably similar to an associated clinical syndrome referred to as macrophage activation syndrome (MAS) which includes high fevers, hepatosplenomegaly, liver/renal dysfunction, coagulopathy, cytopenias, hyperferritinemia, and hypertriglyceridemia, with evidence of hemophagocytosis often noted upon bone marrow biopsy. These characteristics commonly occur in patients experiencing severe CRS, with considerable overlap of cytokine profiles including elevated levels of IFN-γ, IL-6, and IL2RA and in rare cases lead to the development of fulminant MAS in the form of hemophagocytic lymphohistiocytosis. Recent animal models utilizing humanized SCID-beige and SGM3 mouse models have demonstrated that although T cells are the primary source of both IFN-γ and GM-CSF, myeloid cells are the primary producers of inflammatory factors such as IL-6, IL-1, and inducible NOS, which play key roles in the pathogenesis of CRS. Importantly, these same factors have also been shown to drive key components of ICANS such as endothelial activation through the disruption of the angiopoietin (ANG)/TIE2 axis and BBB suggesting the underlying mechanisms for CAR-related CRS likely also drive the development of ICANS via increased BBB permeability, cytokine transit, and vascular pericyte stress.[4] Taken together, we these data suggest that the clinical manifestations of CRS and ICANS are driven by a common pathway, therefore addressing the initial inflammatory insult my result in decreased rates of both.

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5) What has been your experience anecdotally regarding the cost associated with managing severe CRS?

Dr. Shen:

We have heard KOLs in the field say that generally when patients are admitted to the hospital with CRS, they remain in the hospital for 7-10 days and approximately 25% of the patients require admission to the ICU. The cost depends on the institution, but for patients who stay in the hospital for an extended period of time or are sick enough to require ICU care, the cost of managing their toxicities could very easily exceed $56,000.[5]

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—Dr. Angela Shen

Dr. Frigault:

It is difficult to truly capture the "non drug costs" of CAR-T however the current estimates are likely higher than current estimates, largely due to the fact that over ½ of patients who are now being treated with CAR-T would not meet clinical trial eligibility. As the number of patients >65 increases, and require CAR T, we are also locked in with the recent inpatient DRG which does not always cover the true cost to treat, never mind drug acquisition cost. Any relatively low cost intervention that decreases treatment related complications will improve the bottom line for hospitals, especially as newer indications are approved and we continue to sort through the reimbursement aspects of CAR-T.

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6) How valuable would toxicity prophylaxis be and what would be clinical meaningful data?

Dr. Shen:

For the reasons stated above, reliable toxicity prophylaxis would be a key enabler for CAR-T therapies to achieve standard of care status. If there is an agent with favorable safety profile that can be administered around the time of CAR-T infusion, and if it can reliably reduce the frequency and severity of CAR-T induced toxicity such that hospital admissions and use of tocilizumab are significantly reduced, that would lift a lot of weight from the health care system and would help improve accessibility and affordability of CAR-T therapies. CAR-T therapies could be given in the outpatient setting and even in community settings. I imagine the payors would be quite happy with reliable toxicity prophylaxis.

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Dr. Frigault:

Overall a reliable prophylactic strategy would allow for decreased resource utilization and increase the number of patients that could be safely treated at a given time. One of the major hurdles for smaller centers to deliver CAR-T is toxicity management. For instance, in certain countries and centers, ICU beds are held for every CAR-T patient undergoing active treatment. Additionally, many patients are deemed to be high-risk and do not proceed forward with treatment. To meaningfully impact patients with a prophylactic regimen we would ideally see a reduction in grade 2 CRS/ICANS and reduction in tocilizumab utilization. The goal being to demonstrate that you can routinely prevent toxicity that would otherwise necessitate intervention. If successful, providers would be more likely to observe, follow and manage as an outpatient. This approach is often favored by institutions and insurers for all of the above stated reasons. A prophylactic strategy that also delayed onset and reduced severity would also be considered a success given reduction in resource utilization, allowance for outpatient treatment and decreased treatment related morbidity.

In an ideal scenario a patient would be successfully treated in the outpatient setting from start to finish. A prophylactic strategy would be utilized within the first 28 days of treatment (at risk period) and would reduce the rates of CRS (with a focus on grade 2+ CRS) as well as utilization of tocilizumab and steroids. Given the overlapping mechanisms I'd also suspect we'd see a reduction in grade 2+ ICANS. An overall reduction of any CRS/ICANS to <25%, reduction in tocilizumab/steroid utilization to <10% and ability to safely follow patients in the outpatient setting would dramatically change care delivery.

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7) If an agent is shown to be effective in toxicity prophylaxis for currently approved autologous CAR-T therapies, are there other potential applications?

Dr. Shen:

Toxicity prophylaxis would be helpful for autologous CAR-T cell therapies, both approved and upcoming, as well as allogeneic (aka off-the-shelf) CAR-T cell therapies. Allogeneic CAR-T players face CRS and ICANS issues as well. With more options will come greater demand for hospital resources to manage potential toxicities, so reliable tox prophylaxis could play an important role to enabling autologous therapies in development as well as off-the-shelf therapies. Interestingly, cytokine release syndrome is also prevalent with bispecific antibody therapies, such as blinatumomab and others in development. Emergence of toxicities often require interruption of bispecific administration, with tocilizumab being utilized in severe cases. An agent offering toxicity prophylaxis could in theory alleviate the dosing limitations caused by toxicity, and thereby allow the patients to get higher doses or be dosed for a longer duration, all of which could theoretically improve the efficacy of the bispecifics.

"Tocilizumab and Steroids have proven not to be the ultimate solution for management of CRS and ICANS. New, safe therapeutics are still needed to keep patients out of the hospital/ICU and to reduce the financial strain on the healthcare system."

—Dr. Matthew Frigault, and Dr. Angela Shen

Footnotes

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