[MUSIC PLAYING]

KATHLEEN DORRITIE: As mentioned I'm going to be talking a little bit about some of the cellular therapies that have been making headlines the past couple of years. I think the past two years in the oncology world, breakthroughs have-- our big societies have named that cellular immunotherapy or CAR-T therapy as the major breakthroughs for 2017 and even 2016.

So just some objectives. So first to describe what CAR T-cells are and how they work exactly, to discuss some of the unique toxicities of CAR T-cells, and maybe give you some information, just to be aware about, for your own patients who may undergo this therapy. I'll review some of the major clinical trial results and why we're so excited. And then also just very briefly, we'll review what TILs are because we have a pretty big TIL program here as well, which my solid tumor colleagues are developing.

So what exactly are chimeric antigen receptor T-cells? So these are T-cells that are engineered to express an artificial T-cell receptor through which they target specific populations of cells. So in particular, the ones that have been FDA approved thus far and that have made all the news are CAR T-cells targeting CD19.

We've had a lot of development of these CARs. Right now, the ones that are approved and mostly in trials are second generation CARs involving a co-stimulatory domain, which typically has been 4-1BB or CD28. However, third generation CARs and actually even fourth generation CARs are being developed that contain two co-stimulatory domains. And, of course, as this therapy moves forward, the hot area of research is how to make these better.

And so why CD19? So fortunately for us who treat blood cancers, CD19 is expressed pretty exclusively on B-cells and B-cell precursors. However, is not expressed on bone marrow stem cells or on other tissues. And so as you can see, once you get to the pro-B cell stage, you start to acquire CD19. And down below this schematic, you can see just abbreviations for the different type of lymphomas that very commonly express CD19 and for which the CAR-T program has really been focused on.

And so what actually happens to the patient? And on this diagram, which I won't go through in detail, at each point in the process there's opportunities to improve the manufacturing and efficacy of these cells. But essentially the patient initially goes under leukapheresis. So we collect their T-cells essentially. And then those cells are sent off to whichever company is manufacturing the cells for that particular trial or commercial product.

They're stimulated and activated, incubated with cytokines, expanded. Of course, the CAR is introduced. This whole process takes about 18 to 21 days, kind of depending on the company. And then before they're infused back into the patient, they undergo lympho-depleting chemotherapy. So three or four days of fludarabine and cyclophosphamide to make space for the T-cells. However, there are special toxicity considerations. So we do a lot of counseling with patients because this is not a benign therapy.

So the two big categories are cytokine release syndrome, which is really almost like a capillary leak syndrome and neurotoxicity. And so for the cytokine release syndrome, these are typical things you might expect with a big inflammatory response. So fevers, headaches. However, patients can become hypotensive, tachycardic, require pressors, supplemental oxygen, et cetera.

From the neurotoxicity standpoint, this can also vary. So some patients-- I would say, many, many patients will have a little bit of neurotoxicity where they're having some trouble word finding. Interestingly, one of the first signs of neurotoxity that we see is alteration in the patient's signature. So they are constantly being asked to write their signature.

However, some patients can get pretty significant symptoms where they're obtunded. We have not had any patients require intubation. But that has happened certainly.

And the good thing about the neurotoxins is that it is almost universally reversible. So it can take some time. But, of course it's very scary for the family and even for the health team when we see these symptoms.

So in terms of the toxicity management, for the cytokine release syndrome, as you probably would expect, a lot of this is supportive care. So these patients are also neutropenic because of their lymph node depleting chemo. So they're treated like neutropenic fever patients. However, some of them do require lots of fluids, pressors, et cetera.

Tocilizumab is an anti-IL6 antibody, which some of you may have used for rheumatologic disorders. But during some of the earlier studies at UPenn using CAR T-cells, there was one young patient who got very ill after her CAR-T therapy, intubated, multiple pressors. And they were running a cytokine panel and it was found that IL6 was very elevated.

And so one of the physicians there said, wait, there's an antibody targeting IL6. And it's kind of the idyllic story of them calling, and getting this drug, and bringing it to the bedside. And within a few hours, the patient was extubated, off pressors. And it was pretty remarkable.

So far more severe toxicity, patients can also get steroids, high dose steroids. For the neurotoxicity, typically we give steroids depending on which protocol or product it is. Although there's some question as to whether the steroids actually alter the course of the neurotoxicity. If there's a concurrent cytokine release syndrome, we'll give the tocilizumab. But a lot of the neurotoxity management is supportive care. And we do have our neuro-oncologists following. Neurocritical care from Pres B actually will come over if they get to be more significantly symptomatic and whatnot.

Others toxicities to be aware of. So the patients who get CAR T-cell therapy can get very cytopenic. And some of these can be very prolonged. So we have had patients who even three four months out are very cytopenic, requiring transfusions, et cetera. I'm not saying that that's the norm. But it's a possibility.

Some patients-- or most patients-- universally, actually, patients will get B-cell aplasia. And this can be very prolonged. I think I have a graph on a slide in a couple of minutes, just showing how prolonged this is. But I mean months and months after CAR-T, if we do T subset-- or lymphocyte subset analysis, we'll see zero B-cells. So that's something to be aware of. And so what we do check for quantitative immunoglobulins, et cetera.

And then there are some of these other side effects that I've listed here. And then there's the potential for secondary malignancies, et cetera. Although none of these actually been seen. But this is something to keep in mind as we're moving forward in longer term follow-up of these patients.

So this is actually what I was mentioning. So this is just for one of the big studies looking at CAR T-cell infusion for diffuse large B-cell patients. And as you can see, the B-cell plasia can be very prolonged. So these patients, they're on prophylactic antibiotics for a certain amount of time. And then we actually keep them on PCP prophylaxis for several months as well.

So I'm going to go over just some of the clinical trial results, showing why this is such an exciting therapy. I won't go through all of the details. But just to give you an idea why this is making the news and whatnot.

And so the first disease for which we really saw exciting results was ALL. And so the big study that led to the Novartis approval of their product Kymriah was called the ELIANA trial. And this was based out of UPenn. This was looking at a CAR that targeted CD19. There were 88 patients enrolled. 68 actually got their cells. And the median age of note was 12. So this is a younger population, of course,

The very exciting thing was that the complete response was 83%. And I should mention that these were patients who had all failed multiple lines of therapy. So the expected response to a salvage regimen in that setting is very low, probably on the order of about 20% or something. And a proportion of these patients had also had a bone marrow transplant. And still we saw this very high CR rate. And the overall survival probability at six months was near 90%, which is also very unusual and exciting for a young ALL population.

So these are the survival curves from that landmark study. And the thing to make note of actually was that the median duration of remission has actually not been reached at the time of publication. This was an update that was just published in *The New England Journal* earlier this year. So for patients who do achieve a CR, many of them stay in CR and seem to be holding on to their response.

So Sloan Kettering actually reported their data on adult ALL. So the study I was just mentioning was for pediatric patients, as I mentioned. So this was actually in adult ALL patients. And in their series, the CR rate still was 83%.

Now, some of their responses did depend on the amount of disease going in. So I think, as most of us expect, the patients who have a lower disease burden going in seem to do better. But just in general, the majority of pediatric and adult patients will achieve an emerging negative CR. I didn't present all of the data from these studies in the interest of time. But it has become clear that adult patients seem to relapse faster. And so that's just leading us to think of the best way to incorporate CAR-T therapy for ALL in our overall management, meaning that oftentimes we'll go to CAR-T therapy and then as a bridge to a bone marrow transplant.

Disease burden going in seems to correlate with outcome and toxicity, which I didn't discuss. And the pediatric young adult population, so up to age 25, has an FDA-approved product, Kymriah. For adult patients, we can only give them CAR-T therapy for ALL on clinical trial. And so we actually just-- two weeks ago, we infused our first young adult with Kymriah.

So shifting gears to diffuse large B-cell lymphoma, which we see a lot of patients over at Hillman. So this study was looking at axi-cel, or now it's called Yescarta is the kind of brand name. So this was a study looking at relapsed refractory large B-cell patients, so around 80.

There were also some patients who had transformed follicular or primary mediastinal. And these patients all had refractory or relapse within 12 months of an autotransplant. So typically, for large B-cell patients, they get their initial R-CHOP or similar. And then if they relapse, they get a salvage treatment. And then they go for an autologous stem cell transplant. So these patients had failed autologous transplant as well.

And so the overall-- or the objective response rate at a minimum of six months follow-up was 82%. So this is also very high. The CR rate was about 50%. And then 32% had a partial response. Interestingly, the median time to response was actually only one month.

So even if we scan patients at day 30, most of them will have achieved their response by that time. And I say most because certainly we've also seen delayed responses. And just to put it in perspective, the historical control overall response rate to salvage in this setting is about 20%. So this, again, is a big improvement for these patients.

Importantly, the duration of response. So those who achieve a CR seem to hold onto their response. Which, of course, that was a big question when all of this first data came out, is, OK, patients are responding. But how long are they responding?

Juno has their own CAR, 4-1BB CAR. We actually have clinical trials actually with Juno and Kite. But for their product, they had a similar population, relapse refractory, large B-cell. And in terms of their response rates, their best overall response rate was 75% and their CR rate was a little higher at 56%. So one thing that's become clear, and everyone is waiting on, is to see, OK, which one of these products is better, which ones should we be using both from an efficacy standpoint and also from a toxicity standpoint?

And this I'll just skip over. But overall survival at six months is about 88%. And I did not include-- there is one other study from Novartis. Their FDA approved product Kymriah for ALL, it was also FDA approved in the fall for diffuse large B-cell. So there's actually two FDA-approved products for large B-cell lymphoma.

But in general, there have been excellent results given the high risk nature of the study subjects. Importantly, there's been consistent manufacturing. There's very few patients for whom were not able to manufacture CAR-T cells.

Importantly, some patients don't get cells due to disease progression. We have had some patients who get phoresced and then they go downhill very quickly, within a couple of weeks. And they don't even make it to their cells. So I think a big focus now is on moving these therapies earlier.

And there have clearly been differences in toxicity profiles. Even we've seen that in our own studies and using the commercial product. So I think moving forward that'll be important as institutions are deciding which products to use.

So the big questions that remain, should CAR-T be given earlier? So before second, third, fourth, fifth line therapies? Is CAR-T better than autotransplant, which we actually have a study open, that's a head to head CAR-T versus auto. And importantly, the success in large B-cell has now expanded this to be tested in other lymphoma, such as mantle cell, follicular, marginal zone.

So for CLL, some of the initial work, early preclinical work and then pilot studies, were actually in CLL. And we didn't really have much in terms of clinical data until last year. So at ASCO last year, there was a pilot study presented of only 10 patients. So very small numbers, of course.

But these were patients who were not in complete remission for their CLL despite over six months of ibrutinib. And so ibrutinib has been a very successful therapy incorporated into our treatment in the past three to four years. But 89% of patients actually were in a minimal residual disease negative complete remission at three months. So in eight of 10 of the patients. And four of the six had resolution of their lymphadenopathy. So this was very exciting last year at ASCO for those of us who do malignant heme.

Then in September, some data came out of the Hutch with a slightly higher number of patients. So 24 patients with a median of five prior therapies, so very heavily pretreated patients. They all had high risk disease, meaning that they had certain molecular findings or-- I mean patients or family after four or five, I mean I think most of us would consider them high risk anyway. But all of these patients had received ibrutinib. And 19 of the 24 had progressed on ibrutinib.

And so in this study, one month after infusion of CAR-T, 71% overall response rate. And 88% achieved a negative bone marrow.

And again, the big question is, well, are these remissions holding? And so certainly for the patients who achieve a complete remission, and even those who achieve a partial remission, the overall survival, as you can see, is 100% two years out. And, of course, some of this data is still maturing. And there is ongoing trials looking at CLL, which, of course, is a more common type of leukemia than ALL and whatnot. And I'm sure many of you have had patients who have CLL. So this is exciting for the adult oncologists.

So early results are very promising. Pretreatment with ibrutinib actually might enhance CAR-T expansion and response. And that is an ongoing area of clinical research.

And then the last CAR I'll mention is myeloma. And this is probably what we get asked most about from community physicians in oncology, and internists, and family physicians just because of how common multiple myeloma is.

So as I mentioned earlier, CD19 has been a very good target for lymphoid malignancies. However, in myeloma it actually is not a good target. And that's because you lose CD19 by the time you get to the plasma cell stage. And so the bulk of myeloma cells don't have CD19.

So there have been several different antigens being evaluated. And the one that seems to be most promising is BCMA. And so BCMA is present on some B-cells. It's on normal plasma cells and on myeloma cells. And again, importantly, it's not expressed on hematopoietic stem cells or other tissues, which, of course, is important from a toxicity standpoint.

And so last year at ASH, which is coming up actually in December-- so I think a lot of this data will be updated at that time. There were two abstracts that made the news and had people excited.

This first was not as exciting as I would say the second-- but still. This was from UPenn, looking at a BCMA CAR and refractory myeloma. And so not everyone achieved complete remission. But there were one was one patient who had a strict complete remission, two had a very good partial response, one had a partial response.

It kind of depends on which cohort. And by the cohorts, there were different cell doses. And so this was still exciting because it demonstrated that BCMA CARs may work for myeloma. And as I mentioned, there was some efficacy difference between the lower doses of the cells, which I didn't include all those details for this.

And so the second BCMA CAR that was presented was from NCI or Bluebird Bio. So this was their bb2121. In their study there were 21 patients. And there were a median of seven lines of therapy. And all of them had had a prior autologous transplant, which is pretty standard for multiple myeloma. And the overall response rate was 94%, increased to 100% in patients with higher doses.

And so this, of course, was very unexpected and exciting because these patients had failed pretty much everything. Myeloma has been a very exciting world the past five to 10 years. We've had an influx of new agents. However, we all have patients who just keep failing multiple lines of therapy. And then we don't have anything to offer them.

Allogenetic transplant doesn't work very well in myeloma. And so this holds a lot of promise for myeloma patients. But again, of course, these are studies. They're small. And so we definitely need more data.

There are other antigens being evaluated, as I listed below. And so we think that over the next couple of years we'll see myeloma CARs move even further. And there are definitely studies open as well, evaluating myeloma, these different antigens in myeloma.

And this just is one clinical example from blood a few years ago. And so on the left, of course, is the patient's PET scan and all of the black. And you can see in the patient's humerus, femurs, et cetera. And then just two weeks after their BCMA CAR, resolution of disease.

And so where are we going with CAR-T? So certainly there are being continued modifications of the CARs by adding a second and sometimes third co-stimulatory stimulatory domains. Also co-expressing chemokine receptors to improve the cell trafficking. And then also targeting tumor specific antigens derived from intracellular proteins, which is a big area for solid tumors.

And how can we enhance therapeutic benefit because certainly are patients who don't respond? And that is really the big question. Why did they not respond and how can we improve responses overall?

And so I think part of that will be moving cellular therapy earlier. But also combining with other immune therapy, such as checkpoint blockade, which is the hot topic-- well, still is a hot topic for oncology. But three, four years ago was making headlines.

And this is just one example of how a targeted agent, such as ibrutinib-- so Bruton's tyrosine kinase inhibitor-- can enhance efficacy. And this was shown preclinically. And actually has now shown to be the case in clinical studies as well.

And so it's been demonstrated that greater than five cycles of ibrutinib does seem to improve expansion of CAR-T cells during the manufacturing process. In part, this is thought to be related to decreased expression of PD-1 that results from ibrutinib. So it's thought that PD-1 actually can inhibit the expansion of the CARs in vivo. And so actually in the clinical trial that we have open now, there's a cohort looking at patients who are on ibrutinib, continuing their ibrutinib through their CAR-T therapy.

And so there have also been cases where patients have had a partial response to therapy. And then seemed to have progression of disease after their response. And so there have been a couple of case reports showing that checkpoint blockade with PD-1 or PD-L1 can restore CAR-T activity.

So this has been demonstrated both in preclinical models of solid tumors, but also early clinical results in heme malignancies. And so there are many ongoing studies looking at giving either pembrolizumab, nivolumab, et cetera, after CAR-T, either kind of prophylactically or in patients who seem to be progressing after they got their cells.

Just anecdotally, at Hillman, we've had patients who have an initial response, but not really a complete response. And then if we give them pembrolizumab, they achieve a CR. But again, that's still in clinical trials.

Another big area of research is, of course, mitigating toxicity because these are not benign toxicities. And so there is a lot of research ongoing looking at different biomarkers that-- identifying biomarkers that we can use to predict toxicity before it happens. Right now, for most of these patients we're following non-specific things, like CRP and ferritin, which correlate with cytokine release syndrome. But ideally, we really want to have more specific biomarkers and also ways to either incorporate suicide genes or tag the surface of these molecules so that we can shut off the CAR T-cell. So one of the products by Juno actually has an EGFR tag on it. So you could target that using an antibody.

And so this is a very important area. And a lot of companies are trying to also develop, I think, more commercial type assays that can be applied clinically, so that this has a more widespread use just than in clinical trials.

So what about CAR-T therapy in solid tumors? So unfortunately, solid tumors has been more difficult. I think we'll get there. But it's difficult to find an antigen that's very specific to solid tumor cells.

So as I mentioned earlier, we have been looking at intracellular neoantigens. Especially, I think the most promise has actually been seen in, like, glioblastomas. There was some research that came out at ASCO earlier this year. But, of course, people are looking at CARs for lung cancer, pancreatic, et cetera.

And there are also TCRs, which are a little bit different than CARs, that are being evaluated. However, these are HLA restricted. So it's a little bit trickier.

And I'm just going to mention a couple of slides about TILs, partly because as many of you know, we have a very robust immunotherapy group over at Hillman, in particular, melanoma. And so they've really been paving the way here for TIL therapy.

So TILs are the tumor infiltrating lymphocytes in the tumor microbiome environment. And so studies at NIH have shown that the presence of TILs correlates with improved prognosis. And so Steve Rosenberg's lab demonstrated that autologous infusion of TILs can result in durable responses in some solid tumors. So particularly melanoma, but also other immunogenic tumors, such as renal cell, et cetera.

Similar to CAR-T, the cells are collected, expanded, reinfused. The process is a little bit different. But these patients also require reconditioning similar to CAR-T.

And this is just one graph from *Clinical Cancer Research* in 2011. So these were patients with metastatic melanoma. These patients were very heavily pretreated. The different lines are just showing different preparative regimens that they were using in this study.

But if you look at all patients, about 30% were overall survival at three years. However, in those that achieved a complete response, the three year overall survival was 100%. So I think, as many of you know, the prognosis for metastatic melanoma, even with the exciting advances with immune checkpoint blockade, is quite poor. And so this is very exciting.

And then just one other demonstration of the use of TILs. So in cervical carcinoma, this is a smaller study, just looking at HPV TILs in cervical carcinoma And there were a couple of patients who had very-- I think there were only nine or 10 patients in this pilot. But there were two two to three patients who had a pretty dramatic response to TIL therapy. And so that also led the way to expanding this into other types of solid tumors.

So other things to consider. So one of the things I get asked most about is the cost of CAR-T therapy, which as many of you can imagine is very expensive. So the cost of just the cell infusion, depending on which company, is either $300,000 or $475,000, just for the cells. So, of course, we need to look at the big picture here. And that's not including the potential hospitalization, et cetera.

So insurance companies have been all scrambling to figure out coverage. So right now if we have a patient who's getting a commercial product, it's like a single case agreement between UPMC and the insurance company. Medicare is also working to incorporate coverage. And so we're actually expecting by later this year, they're going to have some formal coverage plan.

Some of the companies do have assistance programs, also for things such as housing, travel, et cetera. For the commercial products, patients are required to stay within two hours just for safety reasons for the first 30 days. And so some of them-- of course, it's competition. So they're offering patient assistance and whatnot.

Clinical trials, of course, provide access. And so we always put patient on clinical trial first. And it's important to know that early cost effectiveness analysis shows that there might be benefit to CAR. I mean, of course, that depends on what population you're talking about I think. So clearly a young patient with ALL in their 20s has the potential for many more quality life years than someone who's 70 and has diffuse large B-cell.

So I think the other important thing to note is now that we-- we anticipate that Juno will have an FDA-approved CAR. And their CAR actually has the lowest toxicity thus far. So I think that as these companies are competing, that these costs are going to go down.

And the other thing is that while some of the other larger centers are, of course, manufacturing their own CARs in-house. We haven't started doing that yet. But I think that'll be something in the future as well.

Only specialized centers can administer these cellular immunotherapies. So in the case of CAR-T, it's basically centers that do a bone marrow transplant. But it is very necessary for safety for the patients. It's really been a team effort. And so we work very closely with our ICU staff, our neuro-oncologists, our cardiologists, all of our consultants, to take care of these patients.

So these are just to show you what we have available over at Hillman. And so I work closely with Alison Sehgal. She's one of my colleagues.

And so her and I run all of the CAR-T clinical trials. And so, as you can see, we have kind of a wide portfolio for CAR-T. Our myeloma CAR is not up and running yet, but should be in the next couple of months.

And then these are the three commercial products that-- well, two are approved. And so if a patient doesn't meet the criteria for clinical trial, then we discuss commercial CAR-T with them. And, of course, some of this depends on insurance and whatnot. Although UPMC, unlike other institutions, we have been treating Medicare patients with CAR-T. Some other institutions are not doing that. So I saw a gentleman from Indianapolis, who couldn't get CAR-T there and is coming here.

And then in terms of the cellular therapy program for solid tumors. So metastatic melanoma and UVL melanoma, of course, have TIL trials open, as does head and neck cancer, cervical carcinoma And then we also have, through the phase I program, we're opening TCR, which is similar to a CAR for lung cancer, which should be very exciting.

So I'm hoping in the next five years that we really see a lot more data come out for the use of these in solid tumors because-- certainly I'm a malignant hematologist. But clearly these are much more prevalent cancers. And everyone really wants to see these work in lung cancer, colon cancer, pancreatic cancer, where we have such limited treatment options.

And I just ended with this slide. This is actually one of our own patients, with diffuse large B-cell, who, as you can see, was full of disease at baseline, had failed many lines of therapy, had a huge abdomen. And then during his treatment, actually we can see his abdomen kind of regress.

It was quite amazing. And there was his day 30 scan, six months scan. And he's a year out now and he's still in complete remission. So it's pretty exciting. All right. Thank you.