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Elsevier CME Independent Conference

Highlights of the ASH 2017 Annual Meeting relating to Immunotherapy in Hematological Malignancies

Faculty

Dr Ian Flinn: Hi, this is Dr Ian Flinn, Director of the Blood Cancer Research program at the Sarah Cannon Research Institute in Nashville, Tennessee.

Today I am joined by Dr Dan DeAngelo and Dr Mitchell Smith. It is our pleasure to present the Elsevier CME Independent Conference highlights of the ASH 2017 meeting. Today we are going to focus on immunotherapy and hematological malignancies.

Educational Objectives

This is a list of our educational objectives. I think for most of the people in the audience we understand that there is a tremendous unmet need in hematological malignancies, and just to cite a few examples:

Unmet Needs in Hematological Malignancies

We know that unfortunately for patients with refractory diffuse large B-cell lymphoma the median overall survival is really very poor. It is 6.3 months, and unfortunately only 20% of patients are alive at 2 years.

The experience in ALL is not much better. In fact, in many perspectives it is worse. The median overall survival is 4.5 months in this patient population, and only 10% are alive at 5 years.

While for many patients with AML we think of this as one of the original diseases for which the proof of chemotherapy was important, there has been little or no change in overall survival in large randomized clinical trials conducted in the last 3 decades. Therefore, we certainly need new therapies for patients with a broad array of hematological malignancies.

Immunotherapy in Hematological Malignancies

Immunotherapy in hematological malignancies now has a growing role. We know that the immune system plays an important role in cancer development. For

instance, immunosurveillance has been shown to be important in both the detection and destruction of cancer cells, and that, unfortunately, cancer cells find ways of escaping immunosurveillance. This leads to their propagation and spread.

If you look back historically there have been a number of immunotherapies for treatment of hematological malignancies. For instance, going back all the way to the early '60s, allogeneic transplant is probably one of our first immunotherapies for hematological malignancies. We know this from data that show that not only is replacing the graft of patients with acute leukemia important with a donor's stem cells, but it is the T cells in this graft that form a very important therapeutic option. For instance, patients in whom we do T cell depletion often have an increased rate of relapse after transplant.

Interferon came along in the 1980s. It was an important therapy for hairy cell leukemia at that time, and in the late '90s there was the introduction of the first monoclonal antibody for the treatment of cancer, and this was rituximab, another important immunotherapy.

Current Developments in Immunotherapy: BiTE, DART, and CAR T Cell Therapies

More recently we have seen the introduction of some newer advances in cellular therapy for patients with hematological malignancies. They include two promising areas, including chimeric antigen receptor (CAR) T cell therapies, as well as bispecific T-cell engagers (BiTEs), and we are going to discuss several of these therapies today.

Discussion Outline

This is a brief outline of today's program. I am going to be joined by Dr DeAngelo, who is going to discuss BiTE therapies for patients with a variety of hematological malignancies. Dr Smith is going to review the recent data of CAR T cells in lymphoma, and Dr DeAngelo will also discuss CAR T cells in patients with leukemia.

Finally, we are all going to discuss some of these therapies and how they can be applied to clinical practice.

BiTE and DART therapy in Leukemia

Dr Daniel DeAngelo: My name is Dr Daniel DeAngelo. I am an attending physician at the Dana-Farber Cancer Institute in Boston, and today I will be discussing the data presented at ASH 2017 on some of the bispecific therapy, or BiTE technology, as well as the CAR T cell therapy. These are some of the abstracts that I will be presenting in reference to the BiTE technology.

What are BiTEs?

First the background: BiTEs are bispecific T-cell engagers. It is a newer technology that combines two antibody fragments: the business end, or the variable antigen, of two antibodies that are then joined together as a single polypeptide. The benefit of this is that it redirects the T cells to the site of the disease. In the example I have given with blinatumomab, an anti-CD19 antibody, the variable region is attached to the CD3 portion by a linker domain, thereby bringing the T cell to the site of the disease, and in a patient with relapsed or refractory B-cell acute lymphoblastic leukemia, the T cell then is nearer the lymphoblast.

Two things happen. One is redirected cytotoxic killing of the target or the B lymphoblast, and in addition, you get expansion of the T cells, which will then go out and engage other lymphoblasts.

There are several novel BiTEs that have been in development, not only for B-cell ALL, but also for acute myeloid leukemia, and I will discuss these based on the presentations at ASH.

Abstract 2552: Maintenance Therapy With Blinatumomab in Adults With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL): Overall Survival in Adults Enrolled in a Phase 3 Open-Label Trial

The first presentation was going back to blinatumomab and trying to understand its role in maintenance therapy. Blinatumomab has been approved in the United States for patients with relapsed/refractory Philadelphia-negative acute lymphoblastic leukemia, and it was also recently approved for patients with relapsed/refractory Philadelphia-positive, both in adults as well as pediatrics.

Blinatumomab Maintenance Therapy in ALL (TOWER): Exploratory Analysis From a Phase 3 Trial

In this particular presentation there was an exploratory analysis of the use of blinatumomab as a maintenance therapy, based on the open-label Phase 3 TOWER

trial, which compared blinatumomab to standard-of-care chemotherapy in patients with relapsed or refractory Philadelphia-negative acute lymphoblastic leukemia.

This was a cohort design. These were adult patients, with relapsed/refractory disease, who were treated either in the TOWER study, and these patients who received induction with blinatumomab, followed by up to five cycles of consolidation of blinatumomab, who still had evidence of disease response – these patients were eligible for maintenance therapy.

The design of the original TOWER trial was to try and get as many patients to stem cell transplant as possible, but there were patients who did not go to transplant and proceeded onto maintenance therapy. In fact, 27 patients from the TOWER study received maintenance therapy. This is compared to a cohort analysis from patients who were enrolled in prior Phase 2 or Phase 3 studies of blinatumomab, who received blinatumomab, went into remission, but did not receive maintenance therapy, and the outcomes were compared.

Blinatumomab Maintenance Therapy in ALL (TOWER): Results

Maintenance therapy was given as a 4 week on/2 week off, or 6-week cycle, infusion. Based on the Kaplan-Meier statistical design, the overall survival favored maintenance blinatumomab versus no maintenance therapy in this cohort analysis.

Although the difference did not reach full statistical significance, the hazard ratio was 0.59 with a p value of 0.33. Interpreting this in another way, maintenance therapy was associated with a 41% reduction in the risk of death.

Blinatumomab Maintenance Therapy in ALL (TOWER): Safety

In terms of the adverse events that were seen for patients receiving maintenance therapy, overall it was very well tolerated. Most of the neurologic toxicities as well as cytokine release syndrome occur during the induction phase, which is highlighted here in this table.

During the consolidation phase, cytokine release syndrome and neurologic toxicities are markedly reduced, and then yet again reduced due to the reduction in the tumor burden in maintenance therapy. Maintenance therapy was very well tolerated, as compared to consolidation as well as induction therapies.

Blinatumomab for B-cell Precursor ALL in Patients at Risk for Relapse

One note different from the study, just to alert the audience: the FDA has recently expanded the approval of blinatumomab for patients with minimal residual disease (MRD)-positive B-cell acute lymphoblastic leukemia.

The definition of minimal residual disease that the FDA used to grant approval was based on a level of 0.1% or higher, and this is now the first FDA-approved therapy for patients with MRD-positive ALL.

Abstract 2815: Generation of a Half-Life Extended Anti-CD19 BiTE Antibody Construct Compatible With Once-Weekly Dosing for Treatment of CD19-Positive Malignancies

Let's move onto the next generation BiTEs that were studied and presented at ASH. The first one is a longer-acting anti-CD19 BiTE. One of the difficulties with blinatumomab, which is the standard FDA-approved BiTE specific antibody that targets CD19 and CD3, is that currently it has to be given by continuous i.v. administration. This is due to its short half-life.

At ASH, data were presented on a next-generation anti-CD19 BiTE specific antibody, which has an extended half-life and this has favorable biologic properties, both *in vitro* as well as *in vivo*.

Next-Generation Anti-CD19 BiTE With Extended Half-Life: Results

This next generation extends the half-life of the BiTE, specifically targeting CD19 and CD3, and, therefore, has a much better administration pattern.

The biologic properties of this extended half-life CD19 were studied in this particular abstract. In non-human primates the serum half-life was 210 hours after a single injection. After multiple injections there was a robust depletion of circulating B cells, including B lineage bone marrow cells, and peripheral lymphoid organ B cells. There seemed to be no significant overt signs of toxicity by either clinical or laboratory examination.

Abstract 1354: Evaluation of a FLT3 BiTE for Acute Myeloid Leukemia

Moving on to other BiTE-specific antibodies, a FLT3 BiTE was also presented at ASH, targeting patients with acute myeloid leukemia. Just as a reminder, FLT3 [FMS-like tyrosine kinase 3] is a receptor tyrosine kinase that promotes growth in myeloid progenitor cells. This next-generation half-life extended BiTE-specific antibody targets FLT3 and CD3.

The objective of this abstract and study was to characterize FLT3 expression in primary AML patient samples, and explore the effects of the FLT3 BiTE *in vitro* as well as in *in vivo* models of acute myeloid leukemia.

FLT3 BiTE in AML

Eighty-three percent of primary AML patient blasts were FLT3-positive, and the FLT3 BiTE exhibited potent activity in these human AML cell lines, arguing that it would be a potentially efficacious therapeutic option going into Phase 1 trials in humans.

Abstract 1363: CD33/CD3-Bispecific T-Cell Engaging (BiTE) Antibody Constructs Efficiently Target Monocytic CD14^{+} HLA-DR^{low} IDO^{+} AML-MDSCs

Other BiTEs targeting patients with acute myeloid leukemia: in this abstract this is an anti-CD33/CD3-bispecific antibody. One of the background issues is that these myeloid-derived suppressor cells [MDSCs] that are seen in patients with acute myeloid leukemia have immunosuppressive properties. This may be one of the reasons why patients present with profound pancytopenia.

The accumulation of these MDSCs, as they are called, may hinder the host antitumor response, as well as the efficacy of immunotherapeutic options.

This anti-CD33/CD3 BiTE was developed. Preclinical activity against AML blasts was demonstrated with the objective to determine anti-CD33/CD3 BiTE activity against these CD33-positive AML-myeloid-derived suppressor cells.

Novel Anti-CD33/CD3 BiTE

These cells were purified. They were shown to suppress T-cell proliferation in a concentration-dependent manner. However, in the presence of the anti-CD33/CD3 BiTE, T cells interacted with myeloid-derived suppressor cells, targeting their elimination and potentially overcoming their immunosuppressive effects.

Again, these are three novel approaches using biotechnology in patients with acute myeloid leukemia.

DART Mechanism of Action

Moving onto the last abstract that I would like to present, on flotetuzumab: this is a slightly different compound. It is an anti-CD123/CD3 DART [dual affinity retargeting antibody].

As you recall, the BiTE or bispecific T-cell engager is a single polypeptide, bringing down the variable region of two monoclonal antibodies. In the case of

blinatumomab it was CD19 and CD3. A DART is actually two polypeptide chains that are linked with a disulfide bridge. In the example of flotetuzumab, this is a polypeptide directed against CD123 and another polypeptide directed against CD3, and these two polypeptides are then joined by a disulfide bridge.

Abstract 637: Preliminary Results of a Phase 1 Study of Flotetuzumab, a CD123 x CD3 Bispecific Dart Protein, in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome

This is a novel approach, targeting T cell redirection towards CD123, which is expressed in the vast majority of patients with acute myeloid leukemia and advanced myelodysplastic syndrome.

Flotetuzumab in AML and MDS: Phase 1 Dose-Escalation Study of the Anti-CD123/CD3 DART Flotetuzumab

In this clinical trial that was presented by Geoff Uy from Washington University in St Louis, a Phase 1 study, this was a complicated scenario where a leading dose was administered, followed by multiple other doses, 4 days on/3 days off, for a 28-day cycle.

The lead-in dose was administered either as a one-step or as a two-step process in sequential patients. Then for those patients who had responded and were without significant toxicity, additional cycles could be administered.

Flotetuzumab in AML and MDS: Study Population and Safety

Forty-five patients were enrolled. Almost 90% had acute myeloid leukemia. Eleven percent had advanced myelodysplastic syndrome. This was predominantly an older population of patients with a median age of 64 years.

The maximum tolerated dose was 500 ng/kg/day, and the two-step lead-in dose was associated with less severe cytokine release syndrome than the larger one-step lead-in dose, and this is probably the go-forward approach.

Looking at the toxicities, any grade 3 or higher adverse event was seen in about 40% of patients, with infusion-related or cytokine release syndrome seen in three quarters of patients, or 76%, and the most common symptoms are listed here, which included pyrexia, chills, tachycardia, or hypotension.

Flotetuzumab in AML and MDS: Response Rates

Looking at the results, 14 patients received the maximum tolerated dose of 500 ng/kg/day or higher and were eligible for response assessment. In these patients the overall response rate was 43%, including three patients with complete response, and one patient with complete response but incomplete recovery. Also seen was a morphologic leukemia-free state.

This seems to be a novel approach, using a DART as opposed to a BiTE antibody, for patients with relapsed/refractory acute myeloid leukemia.

Discussion: Position of Bispecific Antibodies in Therapy

The bispecific T-cell engager approach, or BiTE approach, in my opinion is a very promising approach, and at least in our institution blinatumomab has become the standard of care for patients with relapsed/refractory B-cell acute lymphoblastic leukemia who are Philadelphia-negative.

For patients who are Philadelphia-positive, of course, we have the tyrosine kinase inhibitors. But when patients fail those, blinatumomab again emerges as an option.

The question at hand is whether or not blinatumomab should be moved more in the upfront setting. There are on-going trials testing blinatumomab. There is an ECOG 1910 study where patients are randomized to receive blinatumomab after two cycles of induction therapy, asking a question of whether or not minimal residual disease can be reduced, and whether or not this improves event-free and overall survival.

With the new approval of blinatumomab for MRD-positive disease, I think this has changed the way most physicians are thinking about blinatumomab, but in general, how people are thinking about acute lymphoblastic leukemia, and the role for achieving a deep molecular, or at least a deep response, in terms of patients with acute lymphoblastic leukemia. Blinatumomab, owing to the BiTE technology, offers patients and physicians an opportunity to get patients into a deeper remission prior to stem cell transplantation.

This is where I see blinatumomab being used in the future, augmenting standard therapy, as well as a role for, if you will, “mopping up” for patients who are MRD-positive after induction or consolidation therapy.

Discussion: Safety, Management, and Future of Bispecific Antibody Therapies

Of course, there is some logistical difficulty with the administration of blinatumomab. It is a cumbersome 4-week continuous infusion.

For the first cycle, at least in the United States, patients are mandated to be in the hospital for a minimum of 10 days in order to monitor patients for both cytokine release syndrome as well as neurological toxicities.

In our institution we have assigned patients receiving blinatumomab to a particular floor, if you will, where the nurses are very comfortable assessing patients' neurological criteria. Therefore, they know before a patient has severe neurological toxicity so that physicians can be notified and interventions taken.

I think obviously with frequency comes comfort, and I think this is one of the limitations with some of the newer technologies, specifically the immunotherapies, where they have novel toxicities. Most of us know how to handle chemotherapy toxicities, but the immunological toxicities, I think, need to be a little bit more on a learn-as-you-go basis, and this is the approach that we have taken.

T cell redirection has been associated, as I mentioned, with cytokine release syndrome. In our opinion, I think it is best if these patients are treated in an isolated room, or a pod, or a floor where the nurses are very comfortable with this.

Steroids are a very good way of ameliorating some of these cytokine release syndromes, and just to review that, this is fever, chills, sometimes pruritus. Sometimes patients can develop hypotension, which can be severe. Again, early recognition, administration of steroids, and also making sure that the i's are dotted, the t's are crossed – that a patient doesn't have any ongoing infection.

In addition, neurological toxicity is seen in these immunotherapeutic trials, specifically blinatumomab, which is the most experience that we have, and some of these can be very simple as due to confusion, mild dysarthria, but you can see more serious toxicities, including encephalopathy, and sometimes seizure activity. Again, early recognition and early administration of corticosteroids can ameliorate many of the neurotoxic symptoms that can be seen with these BiTE-specific and DART antibodies.

The mechanism of action is a little bit unclear. The thought is that as these T cells are activated they are expanded as part of the process, and that, as a result, these T cells can migrate elsewhere and probably into the central nervous system.

You do see, on spinal fluid exam, evidence for activated T cells in patients receiving a BiTE-specific antibody.

Most of the technology and most of the therapies have been used in patients with B cell ALL, owing to the fact that good immunotherapies are going to remove the target, and if the target is CD19, for example, they are present not only on the diseased lymphoblast, but also on the normal B cells. Patients can, as a result of the long half-life of their immunoglobulins, live with a partial depletion of their B cells. However, depletion of their myeloid cells is somewhat different, as we all know, from the toxicity of our current cytotoxic chemotherapeutic agents. Therefore, BiTE-specific technology against some of the common AML targets like CD33 has been a little bit more difficult.

CD123 is a novel option, where it is present on the vast majority of cells but may still allow for some hematopoietic recovery. The big issue in administering some of the BiTE technology in the CD33/CD123 setting is myeloid suppression, but these need to be integrated, and at least in the next generation we will see some therapies emerging for our patients with relapsed/refractory disease.

Future questions in terms of how this BiTE technology is going to be implemented: as I alluded to, moving these agents more upfront, and really starting to be proactive in the treatment of our patients who are MRD-positive, in terms of targeting them to transplant in a better disease state, with administration of blinatumomab, at least in that case. But other options for patients with myeloid leukemias may also play a role in a similar analogous setting for those patients who are MRD-positive, but need a stem cell transplant.

CAR T Cell Therapy in Lymphoma

Dr Mitchell Smith: I am Mitchell Smith. I am the Associate Cancer Center Director at George Washington University in Washington DC, and today I will be discussing the data presented at ASH 2017 on CAR T cell therapy.

CAR T Cell Therapy: Mechanism of Action

CAR T cell therapy has made a major impact in a fairly short time here, and just to review, CAR T cells are engineered by taking a patient's own T cells, taking them out and modifying them in a culture to produce chimeric antigen receptors on their surface. These modified T cells, which are now targeted to the target of interest, and we are going to talk mostly about CD19 targeted cells today, on the surface of the

B-cell lymphomas, these modified T cells are then expanded and as they are created sent back and returned to the patient by a simple intravenous infusion. They have shown promising activity in many hematological malignancies that are rapidly expanding in scope.

Before the cells are reinfused, patients are generally given chemotherapy – preconditioning or lymphodepleting chemotherapy – to make space for the new T cells to expand and grow.

Abstract 577: Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Today we will be covering several trials, primarily the JULIET trial, and then a number of the ZUMA trials.

CTL019 in DLBCL (JULIET): Phase 2, Single-Arm, Open-Label Study

The JULIET trial was a Phase 2, single-arm, open-label trial using CD19 targeted CAR T cells, called CTL019, assessing the efficacy in relapsed/refractory diffuse large B-cell lymphoma. Eligible patients had relapsed/refractory disease, and had had at least two prior lines of therapy and were not considered eligible for autologous stem cell transplantation.

CAR T cells are manufactured at a central location, one in the US and one in Germany, expanded *ex vivo*, cryopreserved, and shipped back to local study centers for infusion into patients. The study involved 27 centers in 10 countries.

I think a key to the development of this as a viable therapy is the ability to ship cells, get them manufactured, and then ship them back to the site, because the manufacturing is quite complicated and the quality assurance is important, so this needs to be done at central centers. Until these studies we are going to talk about, it hadn't been demonstrated that this could be done outside of a single center.

CTL019 in DLBCL (JULIET): Results

In this trial the best overall response rate was a little over 50% in 81 patients. The CR rate was almost 40%, and this was fairly stable with a response rate at 3 months being 38%, and at 6 months (46 patients eligible at that point) it was 37%.

Six months overall survival was about two-thirds, or 65%, but I think the key here is we really want to get prolonged durable remissions, not just simply prolonged partial remissions.

The toxicity of CAR T cells is a bit unique. One of the things is, the cytopenias here is 27%. A lot of this is from the lymphodepleting chemotherapy. An infection rate of 20%, febrile neutropenia 13%, and the two unusual CAR T cell toxicities – one is cytokine release syndrome, which you see here was 58%, but grade 3/4 together was 23%, and this occurs as the cells expand and release cytokines. It is fairly predictable. It happens in the first few days, usually by days 4 to 7, and we are learning more about it, which I will talk about a bit later.

The other still somewhat unexplained toxicity is neurological adverse events. This can range from mild altered mentation to a general, almost near coma, and it can happen almost at any time. Some of these are delayed. Fortunately, they are almost always reversible over time, but they are quite dramatic at times and can be quite disconcerting to the patient, and more commonly to the patient's family.

In summary, there is a high response rate in a cohort of heavily pretreated patients with relapsed/refractory diffuse large B-cell lymphoma, and they demonstrated the feasibility of centralized manufacturing and distribution back to the site for reinfusion, and that these toxicities, as we learn about them, are manageable.

Abstract 578: Long-Term Follow-Up ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma (NHL)

The other large trial is the ZUMA-1 trial, and we will be talking about several things here.

Axi-Cel in Refractory Aggressive NHL: Multicenter Phase 2 Trial (ZUMA-1)

Axi-cel, which is shortened for the long generic name of this compound: this data had been presented, but it was updated at the meeting, and, again, this is another anti-CD19 CAR T-cell therapy, also in refractory aggressive non-Hodgkin lymphoma, so it is refractory diffuse large B-cell, but there was a cohort of primary and mediastinal B-cell and transformed folliculars.

Patients had an ECOG perform status of 0 to 1. In contrast to the JULIET trial, where the preconditioning was investigator chosen, here everyone got a fludarabine/cyclophosphamide regimen – a slightly higher dose to the typical one you

would get for a mini-allotransplant, or a non-myeloablative allotransplant – for 3 days, and then a 2-day rest before the T cells were infused.

Axi-Cel in Refractory Aggressive NHL (ZUMA-1): Results

Here, again, the overall response rate was very high – 82%. Complete remissions, again, just over half, at 54%. Overall survival at 18 months is, again, about half or 52%, and, again, grade 3/4 AEs: neutropenia, anemia, thrombocytopenia. So a recurring theme, you see cytopenias. For grade 3 or higher cytokine release syndrome – 13% – and neurological events are 28%.

You can see on the graph the response rates in the three cohorts: diffuse large B-cells, primary mediastinal or transformed follicular, and overall.

Again, we see refractory aggressive lymphoma, axi-cel produced durable responses and manageable AEs.

The adverse event management is a learning curve, so the more you do it and you get comfortable with this, the better you can take care of your patients.

Abstract 579: A Comparison of One Year Outcomes in ZUMA-1 (Axicabtagene Ciloleucel) and SCHOLAR-1 in Patients With Refractory, Aggressive Non-Hodgkin Lymphoma (NHL)

The question is how does this compare to what we would expect for such patients? We know that relapsed/refractory diffuse large B-cell lymphoma patients who are ineligible for, or who have already had, an autotransplant, generally do poorly, but if you look in the literature and try to define those numbers, it is actually not easy to find.

Axi-Cel in Refractory Aggressive NHL: Comparison of ZUMA-1 and SCHOLAR-1

Therefore, the SCHOLAR-1 was a meta-analysis to look at how patients did in relapsed/refractory diffuse large B-cell lymphoma. Now SCHOLAR-1, which has been published, was compared with the ZUMA-1 outcomes to try to give a historical presentation of how these outcomes might compare to what was expected.

The researchers took the 101 patients in ZUMA-1, and the 500-odd patients in SCHOLAR-1 and performed a number of analyses trying to define the expected versus the observed events in the two cohorts.

Axi-Cel in Refractory Aggressive NHL: Study Population

This is a bit convoluted because it's historical controls, but here are the data. The ZUMA-1 patients, actually somewhat surprisingly were a little bit older, with more of the patients over 65, and slightly more had stage III or IV disease, and a high IPI of 3 or greater, and three or more prior therapies.

In a sense, the SCHOLAR-1 patients seemed a little bit less heavily pretreated than the ZUMA-1 patients. The caveat is that the ZUMA-1 patients had to be stable enough for several weeks to get onto the trial, so there may be some selection on that end.

Axi-Cel in Refractory Aggressive NHL: Comparison of ZUMA-1 and SCHOLAR-1

When you compare the two, it is pretty clear that the ZUMA-1 population did much better than expected from the SCHOLAR-1 data. The odds ratio for overall response rate was 8-fold higher, the odds ratio for CR was 10-fold higher, and there was a 77% reduction in the risk of death.

Therefore, in general, at least it gives you some confidence that the ZUMA-1 patients were not totally selected, and, compared to what you would expect in the SCHOLAR-1 data, significantly had better outcomes.

Abstract 2825: Marked Re-Expansion of CAR T Cells and Tumor Regression Following Nivolumab Treatment in a Patient Treated With Axicabtagene Ciloleucel (Axi-cel; KTE-C19) for Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

We know that ZUMA-1 and JULIET show that CAR T cells are effective, but not always. And how can we make them better? Here is a case of a patient at the Cleveland Clinic, this was presented by Dr Brian Hill.

The background is that we know that T cells can become exhausted, and checkpoint antibodies can re-energize exhausted T cells, so the question is, is the same event happening possibly in CAR T cell therapy?

We had a patient who progressed through or after the axi-cel treatment on the ZUMA trial and then received nivolumab as a second line, or an additional salvage therapy.

Axi-Cel in Combination with Nivolumab in DLBCL: Case Study

Here is the case, a 46-year-old man with germinal center-type DLBCL. He had high PD-L1 expression, refractory to multiple prior therapies. He received axi-cel in the

ZUMA-1 trial, did have cytokine release syndrome, but, nonetheless, rapidly progressed through the treatment.

He came off the trial and in terms of subsequent therapy we elected to give him nivolumab – when he had a marked regression to the initial dosing of the nivolumab, a good partial remission.

Axi-Cel in Combination with Nivolumab in DLBCL: Results

With the help of Kite [Pharma] we studied CAR T cell numbers. You can see that before the nivolumab he had an adequate number of CAR T cells, similar to what was expected, but immediately after the nivolumab he had a 64-fold increase in CAR T cells. Therefore, a rapid expansion in CAR T cells that then came back more towards baseline, but still much higher at month 3 than you would expect from the median of the ZUMA-1 patients.

Therefore, it suggested that a checkpoint inhibitor might reactivate CAR T cells and induce responses.

Abstract 2826: Phase 1 Results From ZUMA-6: Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Combination With Atezolizumab for the Treatment of Patients With Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Based on that and some other anecdotal cases that have shown up in the literature, there actually is an ongoing trial of the axi-cel CD19 CAR T cells. This trial is called ZUMA-6, looking at the safety and efficacy of adding another checkpoint inhibitor, atezolizumab, to treatment with CAR T cells in refractory DLBCL.

Axi-Cel in Combination with Atezolizumab in DLBCL (ZUMA-6): Phase 1/2 trial

Here is the study design: similarly, low-dose conditioning with a flu/cy regimen, CAR T cells as given in the ZUMA-1 trial, and then atezolizumab given for four doses every 3 weeks starting at various times after the T cell infusion.

Axi-Cel in Combination with Atezolizumab in DLBCL (ZUMA-6): Results

The primary endpoint of the Phase 1 study is, is this safe? What are the dose-limiting toxicities [DLTs]? In fact, in the first six patients no DLTs were observed. You can see there was encephalopathy and neurological events. There was cytokine release syndrome, but nothing out of the ordinary considering the CAR T infusion, and the expansion looks promising in terms of higher CAR T cell levels, and gamma-interferon secretion as a marker of T cell activation.

This is a way to perhaps enhance CAR T cell efficacy in a safe manner, and these studies are ongoing, and you will be seeing more and more of these combined approaches.

In summary, CAR T cells are very active. They are now approved in refractory DLBCL and it appears that at least some of the responses in the 30/40% range are durable. It is a little bit early to call them cures, but we are hopeful that that will eventuate. Thank you.

CAR T Cell Therapy in Leukemia

Dr DeAngelo: Let's discuss the use of CAR T cells for the treatment of patients with acute lymphoblastic leukemia.

Abstract 888: Phase 1 Results of ZUMA-3: KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL)

The ZUMA-3 study was presented at ASH 2017, administering axi-cel in patients with B-cell relapsed/refractory acute lymphoblastic leukemia. These are autologous CARs directed against CD19.

Axi-Cel in Relapsed/Refractory ALL (ZUMA-3): Phase 1 Study

Adult patients were enrolled with relapsed or refractory ALL, with a good performance status and they could have no evidence of graft versus host disease or infection. Patients received either one or two doses of CAR T cells, and just as a reminder, these are autologous CARs derived from the patient.

Axi-Cel in Relapsed/Refractory ALL (ZUMA-3): Safety

Data on 16 patients were presented. The toxicity is depicted on this slide. Most patients had an adverse event. Grade 3 or greater adverse events were typically seen, as in complications of cytokine release syndrome, hypotension, cytopenia, fever, and a decreased platelet count.

Of interest, tocilizumab has emerged as one of the therapies for cytokine release syndrome, and was administered in 94% of the adverse events. Corticosteroids were administered in 75% of those patients who experienced an adverse event.

Axi-Cel in Relapsed/Refractory ALL (ZUMA-3): Preliminary Efficacy

Although the efficacy population was a subset – only 11 patients – the response rate was extraordinarily high. Nine of the 11 patients had a response, for a total overall response rate of 82%, and eight of these nine patients achieved either complete remission with full hematopoietic recovery or complete remission with incomplete recovery, and there was one patient with a leukemia-free state. So there was a proportionally high response rate for this relapsed/refractory population and these responses were durable. In fact, only four patients relapsed in the day 63–168 region.

There seemed to be very similar efficacy, regardless of whether patients received an infusion of 1 x 10^6 CAR T cells/kg or 2 x 10^6 CAR T cells/kg. An enrollment in a lower dose cohort trying to minimize toxicity using 0.5 x 10^6 CAR T cells/kg is ongoing but not reported in this abstract.

Abstract 887: Preliminary Results of UCART19, an Allogeneic Anti-CD19 CAR T-Cell Product, in a First-in-Human Trial (CALM) in Adult Patients with CD19$^+$ Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

A second abstract, a novel approach, used the UCART19 in relapsed/refractory disease. This is different than the available CARs that have been approved. This is an allogeneic CAR, or what we call an off-the-shelf CAR.

UCART19 in Relapsed/Refractory ALL (CALM): Phase 1 Dose-Escalation Trial

In this study adult patients greater than 16 years of age with relapsed or refractory CD19-positive B-cell ALL were enrolled and they received lymphodepletion with fludarabine and cyclophosphamide. Some also received the monoclonal antibody atezolizumab. Then a single dose of UCART19 was administered.

UCART19 in Relapsed/Refractory ALL (CALM): Study Population

Here, we have the demographics of these six patients. Again, this is a small study. Patients were of a predominantly young age, with a median age of 22.5 years. Most of these patients were heavily pretreated. Five of the six had relapsed after an allogeneic stem cell transplant, and did so early. Therefore, this is very high refractory, aggressive disease.

UCART19 in Relapsed/Refractory ALL (CALM): Results

All six patients suffered cytokine release syndrome, with one fatality. But the neurotoxicity seemed to be a little bit better tolerated than our prior experience with autologous CARs. In fact, there was only one neurological event out of six patients, and that was grade 1. There was one skin graft versus host disease. There were a

couple of cases of CMV reactivation. And, important in terms of looking at response again, the CRis that were noted in the prior slide, four of the patients achieved MRD-negative status by day 28.

Therefore, again, very high efficacy, small patient numbers, but these allogeneic CARs may provide options for our patients that the standard autologous CARs just simply cannot provide.

Discussion: CAR T Cell Therapy Approaches for ALL

Where do I think that CAR T cell therapy is best approached for patients with acute lymphoblastic leukemia? There is already an approval for patients under age 25, at second or greater line.

The concern, at least in the standard autologous CAR, is toxicity, number one. Trying to ameliorate the toxicity I think is going to be a user-friendly approach where the more experience the center has with seeing and recognizing toxicities, and, therefore, administering a therapy such as tocilizumab or corticosteroids is going to benefit patients in general, just like when we talk about blinatumomab, trying to minimize toxicities by getting more experience.

However, at least right now I see the CARs at second line, with blinatumomab and inotuzumab monoclonal antibodies having very high single-agent activity. At least in my clinical practice I am really getting CAR T cell therapy for second or third-line relapse.

The big issue is, once a patient goes into remission with CAR cells and is MRD-negative, do you need to bridge a patient to transplant? There is no good study that argues. The ELIANA trial which is the largest study, mostly in pediatric patients, used a CAR with a 4-1BB T cell activation molecule. Very few of those patients went on to a stem cell transplant, and, therefore, the event-free and disease-free survival is predominantly a CAR-only approach. This is in contrast to the study that was published by Park JH and colleagues in the *New England Journal of Medicine* earlier this year, where the approach was to bridge as many patients as possible to transplant.

However, there seemed to be no difference in outcome between those patients who were able to go to transplant versus those patients who did not. Therefore, I think this should be taken on a case-by-case basis. We simply don’t have the experience in adult patients.

I think MRD is one strategy that can be used to allocate patients to or away from transplant. As well as B-cell aplasia and the presence of CARs that are in circulation, persistent CAR, that is patients with persistence of their CAR cells, probably do not need a transplant, versus patients who lose their CARs or develop MRD-positive disease probably should be transplanted as soon as possible.

However, this is an evolving therapeutic discussion that needs to be tested with clinical trials.

Discussion: CAR T Cell Therapy for DLBCL

Dr Flinn: Mitch, there are now two FDA-approved CAR T cells for refractory diffuse large B-cell lymphoma, and probably more approvals on the way. What are the differences between these products?

Dr Smith: There are a lot of potential differences. There are some minor differences in the exact construction of the CAR gene. There are differences in what the cytoreductive therapy is, and so it is a little hard to compare, honestly. When you create these products there are differences in the T cell product from patient to patient – how many CD4, how many CD8 – and if we try to micromanage all of these it is going to be very difficult.

I don't see them ever being compared head-to-head. My take on these is that the results are fairly similar, given that the patient populations are a little bit different, and they are more similar than different.

It is going to be very difficult to know what the optimal treatment is. This will take years of testing to optimize, but right now I think it is more logistics which would define which of these two you might use. I don't think there's a huge difference in efficacy that we can point to at this point.

Dr Flinn: There are some logistical issues and, frankly, there are some financial issues that confront us. At this point what I am hearing is that your institution will probably be driven by these logistical issues, rather than one patient might get one therapy and another patient would get another. Is that correct?

Dr Smith: I think it is very possible. Logistics and insurance approvals may really drive what happens. I think working with different companies will be difficult. It would be nice to keep it with one company because of the logistics of how you process, send and receive these cells. You do have to obviously be very careful that the correct

cells are given back, quality assurance, that they are maintained at the proper temperature, that they are thawed properly. So, there are a lot of logistical issues, and to do it slightly differently for different companies and different products I think will be complex.

I would mostly see an institution selecting one, preferring one company to work with, so that those logistics can be solidified and minimize the chance for errors or problems along the way.

Dr Flinn: Earlier you talked about some of the safety issues that we see with CAR T cells, for instance, the cytokine release syndrome, the neurological toxicities.

We get a number of referrals in for patients for CAR T cells, and, frankly, they are probably not the best candidates for this type of therapy. What is the profile of somebody you think should be referred and should receive this treatment?

Dr Smith: I think one key is that this is not for the faint of heart. These patients can get quite sick. Some of them sail through, but the patients in these trials were very highly selected, good performance status, good cardiac function, and by the fact that it takes 3 weeks to manufacture and QA, and get these cells back, they weren't the patients with the kind of relapsed lymphoma that's doubling in front of your eyes, and so there was some self-selection.

I think especially at the beginning of a new therapy that is potentially toxic we have to be careful and pretty much stick to the patients who are in the trials, who are fairly good performance status patients. Therefore, this is not 'gee, they are not a candidate for a transplant because they are too sick, but I will give them CAR T'. I think many of the same characteristics that would make you think someone is or isn't a candidate for stem cell transplant would be the same characteristics you look for in a CAR T patient.

At least for now. There is a learning curve. In the ZUMA trial the second half of the patients had much less toxicity from cytokine release syndrome because there is a learning curve on how to manage it, early use of steroids, recognizing it, giving anti-IL-6 antibodies. So I think as these evolve we will find better ways to manage them, just like autotransplant went from inpatient for months to now outpatients.

I think it is a rapidly changing field, but right now, I think caution in picking good, healthy, fairly stable patients will be important.

Dr Flinn: Of course, they would have to have fairly good hematopoietic function just to be able to acquire the lymphocytes in order to produce the cells, and so that is often an issue, or can be an issue.

What about bridging therapy? Some studies allow – once the lymphocytes have been acquired through apheresis, and there is that period of time from the manufacture that the patients can be a bit unstable – bridging therapy, meaning giving someone some form of treatment that keeps the disease under control and allows them ultimately to get the therapy. What have you seen in this area? Have you used that in the past, and what do you think ultimately that will be?

Dr Smith: Yes, I think the reason to not have bridging therapy for the trials was really to keep them clean, to make sure that no one would argue 'gee, it was that bridging therapy that was effective rather than the CAR T'. I think for trial design it was important, but in the real world I don't think it is important at all. I think I would definitely favor the use of some bridging therapy.

The problem is, of course, these patients are usually resistant to most treatments, but I do think if you have something that might make sense to control their disease you probably want to stop it a week or so before the T cells are infused. If you are getting the flu/cy that will provide you some response, starting 5 days before the Kite product, the axi-cel. Therefore, there are different ways to manage this, but I think bridging therapy or not was really a trial design, not anything having to do with avoiding it from a clinical standpoint.

Dr Flinn: You have walked us through some of the data in comparison with the SCHOLAR-1 analysis, and put some frame of reference around it. I am convinced from the patients that we have treated that many of these people are alive, and they clearly would not have been alive without this therapy, and so it is, as you have said, not for the faint of heart. It is a difficult therapy to give. Hopefully, that's improving every day, but it brings up the question of maybe using this earlier in the course of the disease, maybe using it instead of transplant, and so there are trials looking at that.

What's your take on that? Do you think that we are going to be using stem cell transplant 5 years from now, or is everyone going to be using CAR T cells?

Dr Smith: I think there will be quite a shift to CAR T cells. When you look at R-CHOP relapsed patients, transplant is not very effective. It is not the 50% we often quote, and patients who relapse within their first year from R-CHOP actually do quite poorly.

I suspect that CAR T will win that direct head-to-head competition and we will be giving CAR T cells for most of the early relapses. If you relapse 2 years out, and there is reasonable chance with autotransplant, I think then that will be a decision to be made depending on the overall efficacy of the CAR T. But I honestly think that CAR T will win in the primary refractory and early relapsed DLBCL, and we will be using it much more than we do today.

Discussion: Future Direction for CAR T Cell Therapy

Dr Flinn: I think that is my bet as well. But there are people, as you showed, that unfortunately progress after this therapy. It is not everyone, in fact it is probably less than half in the refractory arena. You touched upon including checkpoint inhibitors with CAR T cells. Do you think that's going to become standard therapy? The numbers are small now.

What other ways can you think of for improving CAR T cell therapy besides just making it more tolerable and decreasing the toxicity?

Dr Smith: I am not totally convinced about the checkpoint inhibitors. It is certainly an interesting approach that warrants investigation. I think with any new therapy you have to say, why doesn't it work in all these other patients?

In the ALL data we know that some patients downregulate the target, so this may be one of the problems. Therefore, we have to figure out what is the mechanism of resistance? Is it a resistance in the tumor itself, or something with the T cells or their interaction, and I think ultimately it is going to be another case of taking a personalized approach that we need to figure out why it didn't work in this patient, and either, yes, this patient needs to reactivate their T cells with a checkpoint inhibitor; this patient needs to have them amplified with an immune modulator like lenalidomide; or this patient's lymphoma is now resistant and doesn't care about binding CD19, and maybe we need another CD22 CAR; and then finally, the CAR T cells, themselves, there are a whole host of ways to make them more effective.

I think there are a lot of approaches, but what we don't really understand yet is the mechanism of resistance, why it works in some patients and not in more, and as we do that I think we will be able to target our approaches more to make the CAR T cells more effective.

Dr Flinn: Do you think that CAR T cells are going to become more broadly applicable? We know about the data that Dr DeAngelo went over in ALL, but how about

AML, how about other diseases, other hematological malignancies, and for that matter, solid tumors? Where do you see this whole area going?

Dr Smith: I think the most exciting area right now furthest along is probably multiple myeloma, where there are clear targets and efficacy, so I think that is going to come on probably next, along with adult ALL. I don't think there is anything specific about pediatric ALL, so I think adult ALL and myeloma are the next two major ones.

After that the problem is the target. We get spoiled on B cells because we know you can wipe out all your B cells and be fine. That's not so easy to target a myeloid precursor and make someone aplastic forever, and, yes, you got rid of the leukemia. Finding the right target, and that's the same problem with solid tumors, and so the whole problem is finding a tumor-specific marker that will not be a problem if you wipe out all cells that express that target for prolonged periods of time, and that's really the problem. Yes, there are problems getting CAR T access into the tumor and solid tumors, etc. But I think the biggest hurdle right now is finding the right target, so I am a little less confident that that's going to be overcome as quickly.

But the hema-malignancies – myeloma, ALL – interesting in T cell where there's a need, and how would you get a T-cell marker that would not be expressed on the CAR T, but would be expressed on the T-cell lymphoma? That's an area that I think would probably be feasible but needs to be explored. I would say look for myeloma and ALL as the next two hot areas.

Dr Flinn: As you get to these smaller and smaller populations versus the T-cell lymphomas, or even lung cancer, where the antigen is expressed in a small fraction of patients, it certainly increases the complexity and the number of different CAR T cells, or T-cell therapies in general, that you would have to have.

I am impressed, as you are, with the data in myeloma. I have had a number of patients who have unbelievable responses, some of the best responses of their life – deep remissions with the CAR T cells.

Ultimately, if this therapy is going to be so broadly active in patients with hematological malignancies, not even talking about the solid tumors, it seems like we are going to have to get this more out into the community in a broader sense. What would it take? Right now, there is a substantial adverse event profile, but what would it take to get this out of only the tertiary and quaternary centers to be more broadly applicable?

Dr Smith: I think a lot of the logistics has to do with collecting cells – that could be done probably centrally – and reinfusing them, but the key in making them more broadly applicable would be a better understanding and ability to control the toxicity profile. If we can induce prophylaxis in patients against CRS with anti-IL-6, or other anti-cytokine therapies, if we can better understand the neurological toxicity, then the infusion is really not a problem. It is really managing those first few weeks and it is much easier than, say, an allotransplant.

I think the key will be understanding these unusual toxicities, getting them under control, and having strict protocols to prevent and manage them because, especially early on, a few bad outcomes could really put a damper on the enthusiasm. So I think we have to be very careful at the beginning. As it goes forward, and we get better able to predict and manage the toxicities, then I think there are no true logistical barriers to getting it out to the community.

Dr Flinn: However, clearly, even if this were to be done in the community, the community centers would have to gear up to be able to take care of the patients – hopefully, it would be a minority of patients – who had some of these adverse events, but they would have to be really comfortable with managing some of these adverse events.

Dr Smith: You are right. I think one of the things would be some sort of hybrid model where the patients do go to a center for a couple of weeks, get the infusion, are managed maybe as an outpatient living nearby and then go back, because, really, most of the toxicity is short-term and I think at least that might be a bridge to getting it out to the community eventually.

Dr Flinn: Yes. We talked a little bit about ALL. Right now, the therapy is approved for pediatric patients with ALL, but when do you think it is going to get approved for adult patients, and is there any reason to believe that it wouldn't? We know from other studies that it looks like it works pretty well in adult patients.

Dr Smith: Yes, that is why I say I think ALL is high on the list, based on the pediatric data. Adult ALL may be a different disease biologically in some ways, but there is no reason to think that it isn't dependent upon CD19, and should be very effective in adult ALL. We don't do nearly as well as with the pediatric patients, and so the need is clearly there.

Dr Flinn: Some centers, I think, are using this because there are relapses in the ALL patients. Some centers are using it as a bridge to allogeneic transplant, rather

than just being a stand-alone therapy. I guess it really depends on the patient, where they are in the course of their disease.

Dr Smith: The one concern, frankly, about that is using a very, very expensive CAR T as a bridge to another very expensive therapy – allotransplant. It is going to create significant financial toxicity.

Dr Flinn: For sure.

ASH 2017 Key Messages

In conclusion, we have seen a lot of exciting data come out of the most recent ASH meeting for patients with hematological malignancies, using new immunotherapies.

Some of this data includes BiTE therapy, a bispecific therapy where we are redirecting T cells towards the malignant cell and using the immune system to overcome resistance to the cancer.

Another form of that therapy is the CAR T cell therapies, where patients are having their cells modified *ex vivo* and then reintroduced into the patients. Some of this is as a single agent, and some of this is in combination with other therapies. There are a lot of exciting and new treatments for patients with hematological malignancies. I know there will be more data to come in the next few months.

I would like to conclude by thanking Dr DeAngelo and Dr Smith for this discussion.

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