Not for publication or presentation

A G E N D A For conference call and TCT meeting
CIBMTR WORKING COMMITTEE FOR AUTOIMMUNE DISEASES AND CELLULAR THERAPIES
Houston, Texas
Friday, February 22, 2019, 12:15 pm – 2:15 pm

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1. Introduction

The Committee chairs (Peiman Hematti, MD, Sarah Nikiforow MD, and Stefanie Sarantopoulos, MD) and the Scientific director (Marcelo Pasquini, MD) welcomed the committee and started the meeting at 12:17. After the brief introduction, Dr. Nikiforow acknowledged the contributions by the outgoing chair Stephanie Sarantopoulos, MD. Then the minutes from the 2018 meeting in Salt Lake City were then approved by the committee.

Dr. Pasquini then introduced the new incoming working committee co-chair for the Non-Malignant Diseases working committee George Georges, MD from Fred Hutchinson Cancer Research Center.

Dr Pasquini then introduced the Cellular immunotherapy data resources (CIDR) which is part of the cancer moonshot initiative. The initiative involves building outcomes database on cellular immunotherapy to serve as a resource to the community at large. This NCI funded initiative is a program under the Moonshot Initiative to advance cancer research. The CIDR governance structure outlines the development of a working committee to oversee the utilization of this resource for research purposes.

Dr Pasquini then discussed the upcoming restructuring that will affect this working committee, after the launch of the CIDR. As of March 2019, the Autoimmune Diseases and Cellular Therapy working committee will be split based on indication and therapy. The Autoimmune diseases focus will be move to the non-malignant diseases working committee and the cellular therapy will change its focus to cellular immunotherapy for cancer.

2. Accrual Summary (attachment 2)

Dr. Pasquini briefly discussed the status of data that is available for cellular therapy with a brief overview of the milestones since the launch of the CT registry in the summer of 2016. Data in the CT Registry was

operationally divided into three categories, cellular therapy in the context of an HCT, such as donor lymphocyte infusion for prevention or treatment of post transplant complications; cellular immunotherapy for cancer, which includes CAR T-cells and cytotoxic T-cells; and finally regenerative medicine, which includes uses of hematopoietic-derived or other cells for treatment of neurologic, cardiovascular and other illnesses. Additionally, the regenerative medicine group will capture therapies to correct diseases using genetic modified stem cells products. Over 2600 patients who received CT under all categories were reported to the CT registry, mostly receiving DLI after HCT for treatment of disease relapse followed by CAR T cells for treatment of hematologic malignancies. For regenerative medicine, the most common reported indication was for treatment of neurologic diseases. Among CAT-cells, in 2018 the CIBMTR contracted with Kite/Gilead and Novartis to utilize the CT registry infrastructure to capture long term follow up as part of a prospective post approval study to capture long term outcomes on these patients. The introduction of these two products resulted in an increase in the number of reported CAR T cell cases to the CT registry, which now accumulated 646 recipients mostly recipients of a commercial CAR T cell product. The majority of indications mirror the FDA approved indications for these products, including NHL and ALL.

Dr. Pasquini then discussed the accrual of data for the autoimmune disease, which reporting at least from the US remains in low numbers and unchanged, at least since the publication of SCOT trial for SSC and the MIST trial for MS. The CIBMTR worked wit ASBMT on two position statements to assist centers in referencing them to obtain approval from payors.

3. Studies in progress

Dr. Pasquini briefly discussed the studies in progress before we started presenting the proposals. All autoimmune diseases focused studies will be moved to the non-malignant disease working committee.

a. **CT10-01** Donor Leukocyte Infusion versus Second Allogeneic Hematopoietic Stem Cell Transplantation for Disease Relapse after First Allogeneic Stem Cell Transplantation (N Frey/A Loren/D Porter) Manuscript Preparation
b. **CT13-01** Utility of Unmanipulated Donor Lymphocyte Infusion (DLI) for the Treatment of Infections in Allogeneic Hematopoietic Cell Transplantation Recipients (G Akpek, B Omar) Analysis
c. **AC14-01** Long Term Outcomes after Autologous Hematopoietic Cell Transplantation for Rapidly Progressive Systemic Scleroderma (D Farge) Data Collection – deferred
d. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion (DLI) after HLA-haploidentical allogeneic hematopoietic stem cell transplant (V Roy) Data Collection
e. **AC17-01** CD-19 chimeric antigen receptor T Cells with or without hematopoietic cell transplantation for treatment of refractory ALL (S Nikiforow/J Park/M Perales) Protocol Development
f. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (James Yoon/ Edmund Waller) Deferred for 2019
g. **AC18-02** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (George Georges) Deferred for 2019

5. Future/proposed studies

Dr. Pasquini briefly discussed the two autoimmune proposals we received this year. One of which was dropped due to feasibility issues. The committee received 5 Cellular therapy-focused proposals. Dr. Pasquini then explained that the working committee could accept up to two studies this year.

Autoimmune:

a. **PROP 1811-11** To evaluate the outcomes of hematopoietic stem cell transplant with cyclophosphamide and ATG vs total body irradiation conditioning in the treatment of systemic sclerosis (Gul,Khan,Abuali) (Attachment 3)

This study was presented by Zartash Gul who started out by explaining that the hypothesis of this study was that Immune ablation (with cyclophosphamide and ATG) as a conditioning regimen is safer and has better outcomes than TBI based conditioning regimens. There were 112 total patients that met the proposal eligibility criteria most of these cases received either TBI or Cyclophosphamide based conditioning. There were no conflicts of interest to disclose from any of the PI's.

One comment received was regarding how accessible data will be for long term follow up for these cases. Dr. Pasquini mentioned that we will have to retroactively ask sites for follow up data which is always challenging but especially for this study as we will likely need help from rheumatologist at the sites to help in reporting SSC specific outcome data. Dr. George Georges then commented that this hypothesis might not be supported by the current data we have available. The SCOT trial and ASTIS trial have showed that TBI regimen has been superior. Dr. Gul response was that we still need long term follow up data is, so we can answer this question.

Cellular Therapy:

b. **PROP 1809-03** Allogeneic hematopoietic cell transplantation vs chimeric antigen receptor t-cell therapy for DLBCL patients with prior autologous transplant failure or refractory disease (Hamadani, Pasquini, Locke, Gopal) (Attachment 4)

Dr. Hamadani presented this proposal explaining that 40-45% of DLBCL patients relapse after an autologous HCT transplant. The question is are these patients better off with an Allogeneic Transplant or a CAR T cell infusion. The hypothesis is that overall survival in DLBCL patients with a prior autologous HCT failure or refractory disease following CAR-T therapy will be comparable to patients undergoing allogeneic HCT. Dr. Hamadani then explained the data available to study this question based on the accrual summary of patients generated for the proposal. Currently there are 52 CAR-T patients and 446 Allogeneic HCT patients that fit the eligibility criteria for this study. One limitation for this study Dr. Hamadani brought up is that these 52 CAR-T patients may not be available to analyze due to data being embargoed by centers who are using the CIBMTR as a registry for long term follow up. However, if this is the case Dr. Hamadani mentioned that there is the possibility of including cases from other registries that would be willing to collaborate with the CIBMTR for this study. Dr. Hamadani addressed one comment that asked is it fair to compare patients who survived long enough to receive an allogenic transplant against those who received a CAR-T. Dr. Hamadani explained that the same is true though for patients who survived long enough to receive a CAR-T.

c. **PROP 1811-66** Clinical predictors of response and toxicity following CD-19 directed chimeric antigen receptor t-cell therapy in patients with diffuse large b-cell lymphoma (Hossain, Stiff) (Attachment 5)

Dr. Hossain presented this proposal, explaining that he hypothesis is that baseline clinical characteristics of patients impact likelihood of response to CD19 directed CAR-T cell therapy and the risk of associated toxicities. The scientific impact of the proposal will provide clinicians with an objective approach for determining which patients are suitable for CAR-T therapy by identifying who has the highest chance of a response. Also, this study will identify which patient s are at greatest risk of toxicity post CAR-T therapy. Dr. Hossain then discussed the accrual of patients identified for this proposal. There were 214 patients available most of the patients were enrolled in the registry in

2018 so there is limited follow up data for many of these patients. Dr. Nikiforow asked how toxicity is captured in the CIBMTR follow up forms. Dr. Pasquini explained that this is captured on the 3 month, 6 months and annual follow up forms.

d. **PROP 1811-88** Impact of DLI dose on outcomes of relapsed MDS and AML patients who have had an allogeneic transplant from matched related and unrelated donors (Varadarajan) (Attachment 6)

Dr. Varadarajan presented the proposal, the hypothesis states that the dose of DLI from 0.5x10^7 to 1x 10^7 CD3+ cells correlates with an improved overall survival (OS)and relapse free survival (RFS), in patients who have had relapsed MDS and AML after allogeneic transplants. The primary outcome for this study is to determine the overall survival rate at 1-year post DLI comparing four groups of DLI dose range. 1x10^6cells/kg vs. 1x10^6 - 0.5x10^7 cells/kg vs. 0.5x10^7 – 1x10^7 cells/kg vs. >1x10^7 cells/kg. Secondary outcomes include reporting the incidence of pancytopenia post DLI. Dr. Varadarajan then explained that the CIBMTR is the best database to study this question and this is an important question to study as it could lead to the standardization in dosing of DLI. One question asked how this study would be better than CT10-01 which is very similar in concept to this study. Dr. Pasquini explained that this proposal is looking at a more contemporary cohort and is using the new cellular therapy forms which collects more robust data than the data forms we had for the older study.

e. **PROP 1811-141** Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large b-cell lymphoma (Shadman) (Attachment 7)

Dr. Shadman presented this proposal, Dr. Shadman explained that prolonged cytopenia's are not uncommon in practice but the actual incidence is unknown beyond 30 days post CAR-T therapy. He explained that to design interventional trials to overcome cytopenia a benchmark on the actual burden of the problem is needed. The hypothesis states that at least 50% of patients who receive one of the FDA-approved CD-19 targeted CAR-T products for DLBCL have at least grade 2 thrombocytopenia (platelet < 75,000/mm3) or grade 2 neutropenia (<1,500/mm3) 6 months after treatment. The specific aims of this study are to determine the rate/grade of thrombocytopenia at 6 and 12 months after CAR-T therapy. Also, this study aims to determine the rate/grade of neutropenia at 6 and 12 months after CAR-T therapy as well as determining pre and post treatment factors that may be associated with prolonged cytopenia after CAR-T therapy. Dr. Shadman then highlighted the accrual of patients that met the eligibility criteria of the proposal. There were 189 patients eligible most of the cases were infused in 2018 and there was limited follow up data for survivor as a result. One question received asked what is the status of the embargoed data and should there be concern that this data will not be available for analysis and publication? Dr. Pasquini responded that the CIDR and involving industry partners to participate into the studies. Additionally, once the data is sent and reviewed by regulatory agencies then this data will be available for CIBMTR studies.

f. **PROP 1811-109** CAR-T therapy vs autologous transplant in early rituximab failure in patients with diffuse large b cell lymphoma (Shah, Hamadani) (Attachment 8)

Dr. Hamadani presented this study on behalf of Dr. Shah. The Hypothesis of this study states that CAR-T cell therapy improves OS in patients with early Rituximab failure (<12 months) compared to autologous transplant. Dr. Hamadani explained that the primary outcome will be to compare overall survival among patients who relapse within 1 year of initial diagnosis after first-line rituximab-based chemo-immunotherapy who undergo autologous transplant versus those who receive CAR-T cell therapy against CD19. Secondary outcomes will include relapse rates, and rates of non-relapse

mortality. Dr. Hamadani then described the accrued population that matched the eligibility criteria of the proposal 179 patients in the auto cohort and 142 in the CAR-T Cohort. Most of the CAR T cases were infused in 2018 which is a limitation for follow up data.
One comment brought up was the challenge of comparing these two cohorts as the years of patients receiving CAR-T is mostly collected in 2018 and only 18 cases of auto HCT were reported on CRF track in 2017. Dr. Hamadani explained that this is a limitation of this study as we need CRF level data to do this study as not the all the information needed is collected on TED. That said CRF patients are only a subset of the total number of patients that are reported to the CIBMTR. Dr. Hamadani also mentioned that the lack of available for follow up for the CAR-T cohort is also a limitation.

The meeting adjourned at 2:13 pm.

Working Committee Overview Plan for 2019-2020

Study number and Short title	Current status	Goal with date	Total hours to complete	Hours allocated to 6/30/2019	Hours allocated 7/1/2019-6/30/2020	Total Hours allocated
CT10-01: Donor leukocyte infusion versus second allogeneic HCT for disease relapse after first allogeneic HCT	Manuscript prep	Submission – July 19	0	*0*	0	**0**
CT13-01: Utility of donor leukocyte infusion for the treatment of drug-resistant viral or fungal infections in allogeneic HCT recipients: A CIBMTR analysis	Analysis	Published -July 2020	110	110	5	**115**
AC16-01: Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant	Data File Prep	Submitted -July 20	130	80	50	**130**
AC17-01: CD-19 chimeric antigen receptor T Cells with or without hematopoietic cell transplantation for treatment of refractory Acute Lymphocytic Leukemia	Protocol Development	Manuscript Prep -July 20	290	140	80	**220**
AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD	Draft protocol	Manuscript Prep -July 20	310	60	180	**240**
CT19-01: Allogeneic hematopoietic cell transplantation vs chimeric antigen receptor t-cell therapy for dlbcl patients with prior autologous transplant failure or refractory disease	Protocol Pending	Manuscript Prep -July 20	330	0	260	**260**
CT19-02: Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large b-cell lymphoma	Protocol Pending	Manuscript Prep -July 20	330	0	260	**260**

Oversight Assignments for Working Committee Leadership March 2019

Sarah Nikiforow	**CT10-01**	DLI vs Second Allo HCT for relapse
	AC17-01	CD19 CAR T cells without HCT for ALL
	CT19-01	ALLO vs CAR T DLBCL with prior Auto or refractory disease
Peiman Hematti	**CT13-01**	DLI for viral or fungal Infections in Allo HCT
	AC18-01	Effect of SCB and DLI on GVHD incidence
	AC16-01	DLI After HLA-haploidentical allogeneic transplant
	CT19-02	Prolonged Cytopenia Following CD-19 CAR-T Therapy for DLBCL