ELSEVIER

Blood 142 (2023) 4483–4485

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Bendamustine Is Less Toxic Than Fludarabine-Cyclophosphamide-Based Lymphodepletion before CD28-Costimulated CART19 through Reduced Inflammatory Cytokines

Guido Ghilardi, MD[1], Luca Paruzzo, MD[1], Jakub Svoboda, MD[2], Elise A. Chong, MD[3], Alexander Shestov[4], Linhui Chen[1], Ivan J Cohen, PhD[1], Giulia Gabrielli, MD[5], Dwivedy S. Nasta, MD[3], Patrizia Porazzi, PhD[1], Daniel J. Landsburg, MD[3], James Gerson, MD[3], Jordan Carter, MD[3], Stefan K. Barta, MD[3], Rebecca Yelton, BA[3], Raymone Pajarillo, MS[1], Griffin W White[3], Hatcher Ballard, BS[1], Elizabeth Weber[6], Ellen B. Napier, CRNP[7], Emeline R. Chong[3], Joseph A Fraietta, PhD[4], Alfred L. Garfall, MD MTR[2], David L. Porter, MD[3], Michael C. Milone, MD PhD[4], Roderick O'Connor, PhD[4], Stephen J. Schuster, MD[8], Marco Ruella, MD[1]

[1] Center for Cellular Immunotherapies, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[2] Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[3] Abramson Cancer Center, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA
[4] Center for Cellular Immunotherapies, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA
[5] Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA
[6] Cell Therapy and Transplant, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[7] Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[8] Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Introduction: Lymphodepletion (LD) is an integral component of anti-CD19 chimeric antigen receptor T cell (CART19) immunotherapy, creating the proper environment and cytokine milieu for CART engraftment and function. We previously demonstrated that bendamustine (Benda) LD is as effective as standard fludarabine and cyclophosphamide (Flu/Cy) LD prior to 4-1BB-costimulated tisagenlecleucel but is characterized by significantly reduced cytokine-release syndrome (CRS), neurotoxicity (ICANS), and hematological toxicities. However, whether Benda LD is also effective and safe in CD28 costimulated CART19, and the mechanism for the reduced toxicities associated with Benda LD remain unknown.
Methods: We retrospectively evaluated the outcomes of 59 consecutive non-Hodgkin lymphoma patients (pts), including large B cell lymphomas (LBCL, n=48) and follicular lymphoma (FL, n=11), treated with commercial CD28 costimulated axicabtagene ciloleucel (axi-cel) at the University of Pennsylvania between January 2018 and March 2023. Data cut-off was June 30 th, 2023. LD regimens were Flu 30 mg/m ^{2}/day and Cy 500 mg/m ^{2}/day x 3 days or Benda 90 mg/m ^{2}/day x 2 days. LD choice was at the treating physician's discretion, partially determined by Flu shortage. Pts were evaluated for 3-month response (Lugano criteria), survival, and toxicities (ASTCT, CTCAE) in the 30 days after axi-cel infusion. For hematological toxicities, we analyzed lymphocyte, neutrophil, platelet, and hemoglobin levels from the first day of LD to 30 days after axi-cel infusion. For long-term hematological toxicities, we retrieved blood values at 6 months in pts with ongoing remission. Moreover, we analyzed serum samples collected pre- and post-LD (CART19 infusion day) for changes in circulating cytokines (Luminex) and metabolites (Liquid Chromatography/Mass Spectrometry) in a second cohort of 32 pts undergoing CART19.
Results: Of 59 pts, 37 received Flu/Cy while 22 Benda LD. The two groups were balanced for most clinical features. Responses with Flu/Cy and Benda LD were similar, with complete remission rates of 51.4% and 50.0%, respectively. Progression-free and overall survivals were similar in the two LD groups. However, any-grade CRS occurred in 91.9% of pts who received Flu/Cy versus 72.7% of pts who received Benda LD; any-grade ICANS after Flu/Cy occurred in 43.2% and after Benda LD in 18.2% of pts (**Fig.1A**). These results were confirmed in both LBCL and FL cohorts.
Both LD regimens induced profound lymphopenia by the time of axi-cel infusion. However, Flu/Cy LD induced a deeper reduction in median lymphocyte counts (Flu/Cy: 0.00x10 ^{9}/L; Benda, 0.20x10 ^{9}/L). Additionally, Flu/Cy was associated with a higher incidence of neutropenia of grade ≥3 (100.0% vs 54.5%). Consequently, Flu/Cy pts were more likely to develop infections (78.4% vs. 27.3%), and neutropenic fever (78.4% vs. 13.6%) than Benda receiving pts. By evaluating long-term hematological toxicities, 75.0% of Flu/Cy pts did not have lymphocyte recovery to normal values at 6 months compared to 37.5% with Benda LD.

Mechanistically, both Flu/Cy (n=7) and Benda (n=25) LD regimens induced an increase in the levels of cytokines facilitating CART proliferation (IL2, IL7, IL15). Overall, Flu/Cy LD pts had a higher increase in inflammatory cytokine levels compared to Benda LD pts, including a higher increase in the levels of cytokines previously associated with CRS and ICANS (IL15, IL8, and MCP1, **Fig.1B**). Moreover, after LD, several indispensable anabolic metabolites, including carnitine esters, were decreased in pts receiving Flu/Cy. We also found that NADH and nicotinamide riboside, critical elements for cellular redox balance, were reduced in pts exposed to Flu/Cy LD. We speculate that the higher cytotoxicity/cytopenias, induced by Flu/Cy LD, causes a faster utilization of the above-mentioned metabolites in order to reconstitute the hematopoietic cell compartment to physiological levels, resulting in a higher patient susceptibility to additional metabolic stress.

Conclusions: In this retrospective comparison,Benda LD is a safer alternative to Flu/Cy for CART19 immunotherapy with similar efficacy and significantly reduced toxicities. Our data can serve as guidance to clinicians for the selection of the best regimen for lymphodepletion. Our conclusions are supported by our mechanistic studies showing reduced inflammatory cytokines after Benda LD.

Disclosures Ghilardi: *viTToria biotherapeutics:* Consultancy. **Svoboda:** *Adaptive:* Consultancy, Research Funding; *TG Therapeutics:* Research Funding; *ADCT:* Consultancy; *Merck:* Research Funding; *Pharmacyclics:* Consultancy, Research Funding; *Incyte:* Consultancy, Research Funding; *Genmab:* Consultancy; *BMS:* Consultancy, Research Funding; *Atara:* Consultancy; *SEAGEN:* Consultancy, Research Funding; *Astra Zeneca:* Consultancy, Research Funding. **Chong:** *Genentech:* Research Funding; *Abbvie:* Research Funding; *MJH Healthcare Holdings, LLC:* Honoraria; *Novartis:* Honoraria; *BMS:* Honoraria; *Beigene:* Honoraria. **Landsburg:** *Karyopharm:* Membership on an entity's Board of Directors or advisory committees; *Curis:* Research Funding; *Calithera:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Epizyme:* Membership on an entity's Board of Directors or advisory committees; *ADCT:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: Travel funding; *Morphosys:* Membership on an entity's Board of Directors or advisory committees. **Barta:** *Daiichi Sankyo:* Consultancy; *Janssen:* Consultancy; *Acrotech:* Consultancy; *Affimed:* Consultancy. **Garfall:** *BMS:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Data Safety and Monitoring Board; *GSK:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Patents & Royalties, Research Funding; *Legend:* Consultancy, Honoraria. **Porter:** *Mirror Biologics:* Membership on an entity's Board of Directors or advisory committees; *Tmunity:* Patents & Royalties; *Wiley and Sons Publishing:* Honoraria; *Sana Therapeutics:* Consultancy, Current equity holder in publicly-traded company; *National Marrow Donor Program:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *Kite/Gilead:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Genentech:* Current equity holder in publicly-traded company; *DeCart:* Membership on an entity's Board of Directors or advisory committees; *Capstan Bio:* Honoraria; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Bluebird Bio:* Membership on an entity's Board of Directors or advisory committees; *Angiocrine Bio:* Membership on an entity's Board of Directors or advisory committees. **Schuster:** *Genentech:* Consultancy; *Nordic Nanovector:* Other: Scientific Advisory Committee; *Merck:* Research Funding; *Janssen Research & Development:* Research Funding; *Gilead:* Research Funding; *Celgene:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Acerta:* Consultancy. **Ruella:** *viTToria biotherapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Scientific Founder, Research Funding; *Beckman Coulter:* Research Funding; *NanoString:* Consultancy, Research Funding; *GlaxoSmithKline:* Consultancy; *Bristol Myers Squibb:* Consultancy; *AbClon:* Consultancy, Research Funding; *Bayer:* Consultancy.

OffLabel Disclosure: Bendamustine as lymphodepletion regimen (instead of standard fludarabine/cyclophosphamide) before anti-CD19 chimeric antigen receptor T cells immunotherapy.

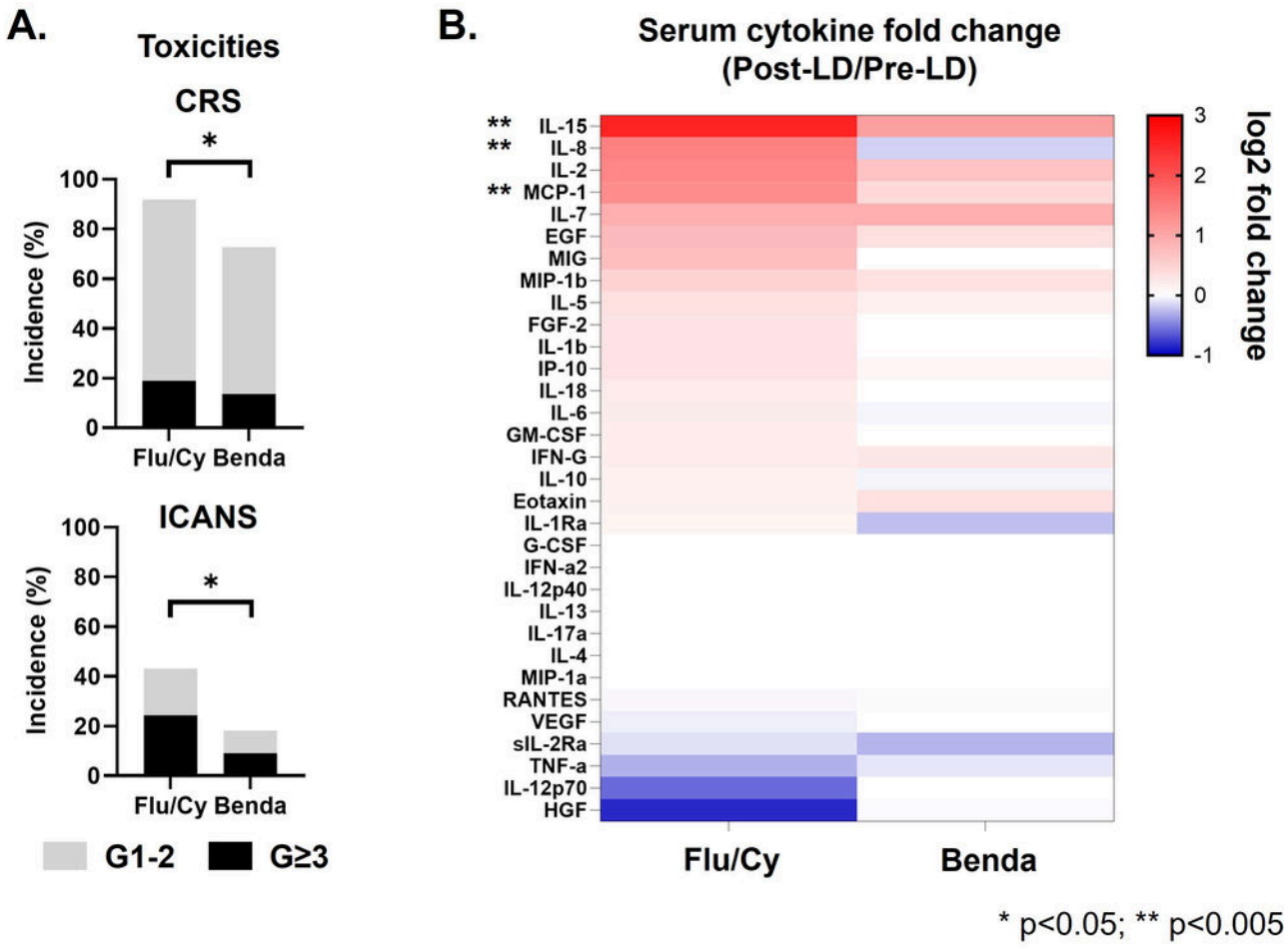

Figure 1

https://doi.org/10.1182/blood-2023-182234