ELSEVIER

Blood 142 (2023) 776–778

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Flares of Acute Graft-Versus-Host Disease: Mount Sinai Acute Gvhd International Consortium (MAGIC) Study

Yu Akahoshi, MDPhD[1,2], Nikolaos Spyrou, MD[3], Daniela Weber[4], Paibel Aguayo-Hiraldo, MD[5], Francis A. Ayuk, MD[6], Udomsak Bunworasate, MD[7], Hannah Choe, MD[8], Matthias Eder[9], Aaron Etra, MD[3], Stephan Grupp, MD PhD[10], Elizabeth O Hexner, MD MSTR[11], William J. Hogan, MD[12], Carrie L. Kitko[13], Sabrina Kraus, MD[14], Pietro Merli, MD[15], Muna Qayed, MD[16], Ran Reshef, MD MSc[17], Tal Schechter-Finkelstein, MD[18], Evelyn Ullrich, MD[19], Ingrid Vasova, MD[20], Matthias Woelfl[21], Robert Zeiser, MD[22], Janna Baez[3], Rahnuma Beheshti[3], Sigrun Gleich[23], Nikolaos Katsivelos[24], Steven Kowalyk[3], George Morales[3], Rachel Young[3], Yi-Bin Chen, MDMS[25], James L.M. Ferrara, MDDSc[3], John Levine, MD[3], Ryotaro Nakamura, MD[26]

[1] Icahn School of Medicine at Mount Sinai, Omiya, Japan
[2] Jichi Medical University Saitama Medical Center, Saitama City, JPN
[3] Icahn School of Medicine at Mount Sinai, New York, NY
[4] Universitiy Hospital Regensburg, Regensburg, DEU
[5] Children's Hospital Los Angeles, Los Angeles, CA
[6] University Hospital Hamburg, Hamburg, Germany
[7] Division of Hematology and Excellence Center in Translational Hematology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[8] Division of Hematology, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH
[9] Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany
[10] Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA
[11] Division of Hematology/Oncology, Department of Medicine, University of Pennsylvania, Philadelphia, PA
[12] Division of Hematology, Mayo Clinic, Rochester, MN
[13] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Vanderbilt University, Nashville, TN
[14] Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany
[15] Department of Pediatric Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Catholic University of the Sacred Heart, Rome, Italy
[16] Emory University, Atlanta, GA
[17] Columbia University Medical Center, New York, NY
[18] The Hospital for Sick Children, Toronto, CAN
[19] Experimental Immunology, Department for Children and Adolescents Medicine, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany, Frankfurt Am Main, DEU
[20] University Hospital Erlangen, Prague 2, CZE
[21] Department of Pediatrics, University Hospital Würzburg, Würzburg, Germany
[22] University Medical Center Freiburg, Freiburg, Germany
[23] University of Regensburg, Regensburg, DEU
[24] Icahn School of Medicine At Mount Sinai, New York, NY
[25] Massachusetts General Hospital, Boston, MA
[26] Hematologic Malignancies and Stem Cell Transplantation Institute, City of Hope National Comprehensive Cancer Center, Duarte, CA

[Background]
The current standard first-line treatment for acute graft-versus-host disease (GVHD), systemic high-dose steroids, induces clinical responses in a majority of patients. Flares of GVHD after initial improvement often occur during tapering or discon-

tinuation of immunosuppression. There is no consensus regarding the definition of GVHD flare and little has been published regarding its natural history.

[Methods]

We retrospectively evaluated clinical data and blood samples from 968 allogeneic hematopoietic cell transplantation (HCT) recipients from 23 Mount Sinai Acute GVHD International Consortium (MAGIC) transplant centers who achieved complete response (CR) or very good partial response (VGPR) within 4 weeks of acute GVHD treatment between 2014 and 2021. VGPR was defined as the complete resolution of acute GVHD manifestations except residual stage 1 skin disease. Flares were defined as a recurrence of acute GVHD after achievement of CR/VGPR if (1) patients had an increased symptom severity of at least 1 organ stage; (2) received intensified treatment (increase in steroid dose $\geq$ 0.25 mg/kg or initiation of additional systemic immunosuppression); and (3) had no prior history of primary disease relapse or donor lymphocyte infusion preceding the flare. Serum samples obtained at the time of CR/VGPR and at the time of flares were analyzed for ST2 and REG3α concentrations that generated MAGIC algorithm probabilities (MAPs) resulting in previously validated Ann Arbor (AA) scores (1, 2, and 3).

[Results]

The median recipient age at HCT was 55 years (range: 0 to 79); 18.6% of patients had grades III-IV acute GVHD before CR/VGPR. The median maximum daily dose of corticosteroids before CR/VGPR was 1 mg/kg methylprednisolone equivalent (range, 0.1 to 3.2 mg/kg). Flares developed within 6 months following CR/VGPR in 210/968 (21.7%) patients with a median onset of 28 days (range: 2 to 448). Symptom severity at the onset of flare symptoms varied widely (grade I: 22%; grade II: 38%; grade III-IV: 41%) and the development of a flare was associated with a five-fold increase in NRM (hazard ratio [HR], 4.84 [95% CI, 3.19-7.36], $P < 0.001$) when considered as a time-dependent covariate in a multivariate regression model. The large majority of non-relapse deaths after flares (54/71, 76%) were due to acute GVHD or complications from its treatment. The AA scores at the time of first CR/VGPR successfully stratified patients for risk of six-month NRM (AA1: 5%, AA2: 11%, AA3: 34%, $P < 0.001$) (Figure A). Increasing AA score at CR/VGPR was also associated with significantly increased risk of GVHD flares (Figure B). Not only did the risk of flare increase with each rising AA score, but the number of patients with severe (grade III/IV) symptoms at flare onset also increased (AA1: 34%, AA2: 43%, AA3: 54%). We next generated a multivariate regression model of risk factors for the development of flares. High AA scores at the time of CR/VGPR (AA2: HR, 1.81 [95% CI, 1.32-2.48], $P = 0.001$; AA3: HR, 3.14 [95% CI, 1.98-4.98], $P < 0.001$), HCT from HLA mismatched unrelated donor (HR, 1.74 [95% CI, 1.00-3.02], $P = 0.049$), and interestingly, rapid achievement of CR/VGPR from the time of initial treatment ($\leq$14 days) (HR, 1.84 [95% CI, 1.21-2.80], $P = 0.004$) were all identified as significant risk factors. Meanwhile, no other transplant, GVHD, or treatment characteristics associated with the development of flares including maximum GVHD severity, maximum steroid dose, and use of additional immunosuppressive agents other than steroids before CR/VGPR. AA scores measured at the onset of flare symptoms in 98 patients also predicted six-month NRM (AA1, 6%; AA2, 19%; AA3 42%, $P = 0.01$).

[Conclusion]

Despite advances in treatment, flares of GVHD symptoms following excellent (CR/VGPR) responses still occur in over one fifth of patients in current practice and are associated with a five-fold increase in six-month NRM. AA scores from serum biomarkers predict outcomes despite the absence of symptoms, suggesting that MAGIC biomarkers detect subclinical damage to GI crypts that can drive later recrudescence of clinical GVHD. Measurement of the MAP at the time of response to GVHD treatment may thus help to risk-stratify tapering strategies of immunosuppressive therapy.

Disclosures Choe: *MJH Life Sciences:* Honoraria; *Incyte:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Receipt of equipment, materials, drugs to institution; *NIH National Cancer Institute:* Research Funding; *Opna:* Other: Receipt of equipment, materials, drugs to institution, Research Funding; *Actinium Pharmaceuticals:* Other: Support for attending meetings and/or travel. **Grupp:** *Juno:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Research Funding; *Jazz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Vertex:* Consultancy, Research Funding; *Kite:* Research Funding; *CBMG:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cellectis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Research Funding; *Adaptimmune:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cabaletta:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Kitko:** *Horizon:* Membership on an entity's Board of Directors or advisory committees. **Kraus:** *Jazz Pharmaceuticals:* Honoraria, Other: Support for meeting attendance; *BMS:* Honoraria, Other: Support for meeting attendance; *Gilead:* Other: Support for meeting attendance; *LinkCare:* Honoraria; *AstraZeneca:* Speakers Bureau; *Janssen:* Honoraria; *Pfizer:* Honoraria. **Merli:** *Miltenyi:* Speakers Bureau; *Jazz:* Membership on an entity's Board of Directors or advisory committees; *Sobi:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Speakers Bureau. **Qayed:** *Novartis:* Honoraria; *Vertex:* Honoraria. **Reshef:** *Orca:* Consultancy; *CareDx:* Research Funding; *TScan:* Consultancy, Research Funding; *Regeneron:* Consultancy; *Instil Bio:* Consultancy; *Incyte:* Consultancy, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Atara Biotherapeutics:* Consultancy, Research Funding; *Gilead Sciences:* Consultancy, Honoraria, Other: Travel support, Research Funding; *Synthekine:* Consultancy, Research Funding; *Bayer:* Consultancy; *Precision Biosciences:* Research Funding; *J&J:* Research Funding; *Jasper:* Consultancy; *Capstan:* Consultancy; *MidaTech:* Consultancy; *Bristol Myers Squibb:* Honoraria, Research Funding; *Allogene:* Consultancy; *Quell Biotherapeutics:* Consultancy; *Sanofi:* Research Funding; *Immatics:* Research Funding; *TCR2:* Research Funding. **Ullrich:** *Phialogics:* Honoraria; *BMS:* Honoraria. **Zeiser:** *VectivBio:* Consultancy; *Medac:* Honoraria; *Sanofi:* Consultancy, Honoraria; *MNK:* Consultancy, Honoraria; *incyte:* Consultancy, Honoraria; *novartis:*

Consultancy, Honoraria, Research Funding. **Ferrara:** *Viracor:* Patents & Royalties: GVHD biomarker patent.. **Levine:** *Editas:* Consultancy; *Sanofi:* Consultancy; *X4 Pharmaceuticals:* Consultancy; *Genentech:* Research Funding; *Incyte:* Research Funding; *Mesoblast:* Research Funding; *Viracor:* Patents & Royalties: GVHD biomarker patent.; *Kamada:* Consultancy; *Equillium:* Consultancy; *Bluebird Bio:* Consultancy; *Mesoblast:* Consultancy; *Inhibrx:* Consultancy; *Incyte:* Consultancy. **Nakamura:** *Leukemia & Lymphoma Society:* Other: grant reviewer; *Miyarisan:* Research Funding; *NCTN Lymphoma Steering Committee:* Membership on an entity's Board of Directors or advisory committees; *NCCN:* Other: guideline panel for HCT; *BMT CTN Steering Committee:* Membership on an entity's Board of Directors or advisory committees; *Blue Bird:* Consultancy; *Sanofi:* Consultancy; *Mt. Sinai:* Other: Acute GVHD; *International Consortium:* Other: consortium chair; *Omeros:* Consultancy; *Napajen:* Consultancy; *Jazz Pharmaceuticals:* Consultancy, Other: research collaboration.

https://doi.org/10.1182/blood-2023-181900