ORAL PRESENTATIONS

SESSIONS A THROUGH N

SESSION A: LATE EFFECTS, SUPPORTIVE CARE AND QUALITY OF LIFE

7

Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome with Multi-Organ Dysfunction: Final Results from a Pivotal, Historically Controlled, Phase 3 Trial

Paul G. Richardson [1], *Nancy A. Kernan* [2], *Joel A. Brochstein* [3], *Shin Mineishi* [4], *Sally Arai* [5], *Stephan A. Grupp* [6], *Eva Guinan* [7], *Paul L. Martin* [8], *Gideon Steinbach* [9], *Amrita Krishnan* [10], *Eneida R. Nemecek* [11], *Reggie E. Duerst* [12], *Joseph H. Antin* [1], *Leslie Lehmann* [13], *Alfred P. Gillio* [14], *Rajinder Bajwa* [15], *Maja Miloslavsky* [16], *Robin Hume* [16], *Massimo Iacobelli* [17], *Bijan Nejadnik* [16], *Alison L. Hannah* [16], *Robert J. Soiffer* [18].
[1] *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA;* [2] *Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY;* [3] *Cohen Children's Medical Center of New York, New Hyde Park, NY;* [4] *Bone Marrow Transplantation Program, University of Alabama, Birmingham, AL;* [5] *Stanford University Medical Center, Stanford, CA;* [6] *Children's Hospital of Philadelphia, Philadelphia, PA;* [7] *Center for Clinical and Translational Research, Dana-Farber Cancer Institute, Boston, MA;* [8] *Pediatric Blood and Marrow Transplantation, Duke University Medical Center, Durham, NC;* [9] *University of Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle, WA;* [10] *City of Hope, Duarte, CA;* [11] *Pediatric Blood & Marrow Transplant Program, Department of Pediatrics, Doernbecher Children's Hospital and Oregon Health & Science University, Portland, OR;* [12] *Division of Hematology, Oncology and Stem Cell Transplantation, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL;* [13] *Department of Pediatric Hematology/Oncology, Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA;* [14] *Institute for Pediatric Cancer and Blood Disorders, Hackensack University Medical Center, Hackensack, NJ;* [15] *Bone Marrow Transplantation, Nationwide Children's, Columbus, OH;* [16] *Jazz Pharmaceuticals, Inc., Palo Alto, CA;* [17] *Formerly Gentium SpA, Villa Guardia, Italy;* [18] *Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA*

Introduction: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of stem cell transplantation (SCT). Severe cases, defined by multi-organ dysfunction (MOD), may be associated with >80% mortality. There is no FDA-approved treatment for VOD/SOS. Here we present the final analysis of day+100 survival and day+100 complete response (CR) of the pivotal phase 3 trial of DF in VOD/SOS with MOD, including additional data obtained at the request of US health authorities.

Methods: This was a multicenter, open-label, phase 3 historical control (HC) study assessing DF. Eligible patients (pts): Baltimore criteria (bilirubin ≥2.0 mg/dL and ≥2 of: hepatomegaly, ascites, 5% weight gain) by day +21 post-SCT, plus MOD (renal and/or pulmonary dysfunction) ≤day +28 post-SCT. Exclusion criteria: severe liver or gut graft-versus-host disease, clinically significant bleeding, or need for ≥2 pressors. HC pts' medical charts were sequentially reviewed starting 6 months prior to each site's DF use; a blinded medical review committee made the final determination of unequivocal VOD/SOS with MOD. DF dose: 25 mg/kg/d, 2-hour IV infusions q6h x4. Recommended treatment duration: ≥21 days. Primary endpoint: day +100 survival. Day +100 CR was a secondary endpoint. Treatment difference in survival and CR rates and their 95% confidence intervals were estimated using propensity score adjusted estimates.

Results: There were 102 pts in the DF group and 32 HC cases. Baseline characteristics were similar: mean age (26 and 25 years; 43% and 44% ≤16 years), allogeneic graft (88% and 84%), prior SCT (13% and 9%), ventilator- and/or dialysis-dependent at study entry (33% and 22%), myeloablative conditioning (87% and 94%), and most common underlying diseases (acute leukemias: 45% and 47%), respectively.

Day +100 survival in the DF and HC groups was 38% and 25%, respectively (propensity-stratified difference in survival: 23.0% [95.1% CI, 5.2−40.8, $P = .0109$]). Observed day +100 CR rates were 25.5% and 12.5% (propensity-stratified difference in CR: 19.0% [95.1% CI, 3.5−34.6, $P = .0160$]), respectively. In the DF group, 45% had an adverse event (AE) and 21% had a serious AE at least possibly related to study drug. Percentages of pts with ≥1 AE leading to death were similar between DF and HC pts (64% and 69%), as were hemorrhagic AEs (64%, 75%) and hypotension (39%, 50%).

Conclusions: Based on observed study data and using a propensity-adjusted rate difference estimator, DF-treated pts had a 23% improvement in survival by day +100 and 19% improvement in CR rate. Overall hemorrhage and fatal AE incidences were similar between groups; AEs were consistent with those expected in this critically ill population.

Support: Jazz Pharmaceuticals

8

Defibrotide for Prophylaxis of Hepatic Veno-Occlusive Disease in Pediatric Hematopoietic Stem Cell Transplantation: Subanalysis Data from an Open-Label, Phase III, Randomized Trial

Selim Corbacioglu [1], *Ansgar Schulz* [2], *Petr Sedlacek* [3], *Bernd Gruhn* [4], *Simone Cesaro* [5], *Peter Bader* [6]. [1] *University of Regensburg, Regensburg, Germany;* [2] *Universitatsklinikum Ulm Klinik fur Kinder, Ulm, Germany;* [3] *Dept of Ped Hem & Onc, Teaching Hospital Motol, Prague, CZ, Czech Republic;* [4] *Department of Pediatrics, Jena University Hospital, Jena, Germany;* [5] *University of Padova, Padua, Italy;* [6] *Stem Cell Transplantation and Immunology, Klinik für Kinder und Jugendmedizin, Frankfurt, Germany*

Introduction: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of stem cell transplantation (SCT). It is associated with patient and transplant-related risk factors, such as prior therapies, underlying diagnoses, and conditioning regimen. Defibrotide (DF) is approved in the European Union for treatment of severe hepatic VOD/SOS post-SCT; it is available in the United States through an expanded-access study. In a randomized clinical trial, DF prophylaxis for VOD/SOS in high-risk pediatric patients undergoing SCT reduced overall VOD/SOS incidence by day +30 post-SCT. We report subgroup analyses of VOD/SOS incidence from this trial in patients with specific baseline VOD/SOS risk factors.

Methods: This was a phase 3, multicenter, open-label, randomized, controlled trial in patients <18 years, with myeloablative conditioning before allogeneic or autologous SCT and ≥1 VOD/SOS risk factor. VOD/SOS was diagnosed using modified Seattle criteria (>5% weight gain). Patients were randomized to standard care with or without DF prophylaxis (25 mg/kg/day, 4 divided 6.25 mg/kg infusions). Osteopetrosis was a stratification variable. DF began the same day as conditioning, continuing for 30 days post-SCT or ≥14 days for patients discharged from hospital before day +30 post-SCT. Control patients developing VOD/SOS received DF treatment. Primary endpoint: day +30 incidence of VOD/SOS post-SCT.

Results: The intent-to-treat population included 356 patients: 180 randomized to DF prophylaxis and 176 in the control group. Mean (SD) age: 6.6 (5.3) years. 40.7% of patients were female. Demographic and clinical characteristics were well-matched. Most common risk factors: busulfan/melphalan conditioning (58%) and preexisting liver disease (27%). VOD/SOS occurred by day +30 post-SCT in 22 (12%) patients in the DF prophylaxis group vs 35 (20%) in the control group. Rates of VOD/SOS in osteopetrosis patients were 14% in the DF prophylaxis arm vs 67% in the control arm. VOD/SOS rates by day +30 were reduced by ≥50% in the DF arm vs the control arm in patients with hemophagocytic lymphohistiocytosis (0%, 40%), second myeloablative transplantation (8%, 17%), and prior gemtuzumab treatment (18%, 40%, respectively). Differences in VOD/SOS rates were lowest for adrenoleukodystrophy (ALD, no cases) and prior abdominal irradiation (11% vs 13%, respectively). The overall AE incidence was similar between patients receiving defibrotide prophylaxis (80%) and control arm patients (80%).

Conclusions: Across risk-factor subgroups, the rate of VOD/SOS was lower in patients receiving DF compared with controls (except ALD: no VOD/SOS in either group). Although the total numbers of patients with these risk factors were small, these between-group differences are of clinical interest and should be further explored.

Support Jazz Pharmaceuticals

9

Risk Factors for Human Papilloma Virus Reactivation in the Genital Tract of Female Stem Cell Transplant Survivors

Dana Shanis [1], *Prathima Anandi* [2], *Caitlin Grant* [3], *Averyl Bachi* [4], *Nina Vyas* [5], *Priyanka A. Pophali* [6], *Eleftheria Koklanaris* [2], *Sawa Ito* [2], *Bipin N. Savani* [7], *A. John Barrett* [2], *Minoo Battiwalla* [2], *Pamela Stratton* [8]. [1] *NICHD, NIH, Bethesda, MD;* [2] *Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD;* [3] *Howard Community College, Columbia, MD;* [4] *Newcastle University, NE1 7RU, United Kingdom;* [5] *David Geffen School of Medicine at UCLA, Los Angeles, CA;* [6] *Hematology Branch, National Heart, Lung, and Blood Institute, NIH, Bethesda, MD;* [7] *Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN;* [8] *Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD*

Human Papillomavirus (HPV) infection inducing cervical, vaginal, and vulvar warts and leading to cervical cancer is a significant risk for women after stem cell transplantation (SCT). Determining risk factors and the course of HPV disease in these women will clarify screening and treatment practices. Prior studies in transplant survivors have focused on cervical dysplasia alone and identified graft–versus-host-disease (GVHD) as a risk factor but time to HPV disease, history of HPV pre-transplant and occurrence of multifocal or persistent HPV warrants study.

In a prospective long-term study after SCT, gynecologic history and assessment, cervical cytology and HPV testing were obtained with colposcopy and surgery as indicated. Results of testing/treatment performed by other gynecologists were ascertained. Prior HPV disease, marital status, age, ethnicity, diagnosis, transplant conditioning, genital GVHD (gGVHD), chronic GVHD (cGVHD) and immunosuppression treatment (IST) >3years were assessed for their association with extent, persistence and severity of any genital HPV disease. Backward stepwise logistic regression modeling was used for multivariate analyses.

82 female HLA-identical sibling SCT survivors (> 1 year and who had gynecology testing) were studied, with a median follow up of 9.4 yr. The median age was 36 yr (range 10-68); acute leukemia was the most frequent diagnosis (45%); 93% were myeloablative ex-vivo T-lymphocyte depleted. The cumulative rate of genital HPV infection at 1, 3, 5, 10 and 20 years was 4.8, 14.9, 28.1, 36.7 and 39.7%, respectively. 15 (18%) women had an abnormal pap prior to SCT, which was associated with risk of post-SCT HPV (OR=6.5, p=0.008), and was the strongest risk factor for persistent HPV (OR=23.2, p<0.001). 56 (68%) women had cGVHD (25 limited, 31 extensive); 21 (26%) had gGVHD. Having either extensive cGVHD or gGVHD was associated with increased risk of any HPV disease (OR= 5.7 p=0.002) and a higher risk for severe dysplasia (CIN II-III / VIN II-III; OR= 13.1 p=0.017). 11 (13%) women underwent hysterectomy before or after transplant, which was associated with increased risk of multifocal HPV (OR= 7.9 p=0.01).

The doubling of HPV rates and its association with extensive cGVHD or gGVHD in transplant survivors likely reflects HPV reactivation and suggests a role for immune dysregulation. The kinetics of reactivation suggest a wide window for HPV vaccination, which may reduce this risk of reactivation. Gynecologic history may identify women who warrant frequent monitoring. As persistent HPV disease can progress, women benefit from regular gynecologic follow-up.