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Defibrotide for the Treatment of Patients with Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome with/without Multi-Organ Dysfunction Following Chemotherapy: Subset Analysis Results from an Ongoing Expanded Access Program

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**Introduction:** Hepatic veno-occlusive disease, or sinusoidal obstruction syndrome (VOD/SOS), is a potentially life-threatening complication of hematopoietic stem cell transplant (HSCT) conditioning regimens. There is a known risk in patients (pts) post-chemotherapy (CT) in a non-HSCT setting. Severe hepatic VOD/SOS (VOD with multi-organ dysfunction [MOD]), may be associated with >80% mortality. DF is approved for treatment of severe hepatic VOD/SOS in adult and pediatric pts in the European Union; DF is available through an expanded-access protocol in the United States.

**Methods:** Originally, eligible pts had hepatic VOD/SOS by Baltimore criteria post-HSCT and MOD (renal and/or pulmonary dysfunction). The protocol was later amended to include (1) post-CT pts with hepatic VOD/SOS; (2) pts with hepatic VOD/SOS without MOD, and (3) VOD/SOS per modified Seattle criteria. Enrolled pts received DF 25 mg/kg/d in 4 divided doses for a recommended duration of ≥21 days. Here, we describe efficacy and safety results with DF for pts that developed VOD/SOS post-CT.

**Results:** Of 642 pts who developed VOD/SOS with ≥1 dose of DF, 69 received CT without HSCT for malignant treatment; 52% (n=363) had MOD, 48% (n=33) did not. Median age: 8 years (range, <1 month–58.0 years); 55 pts (80%) were ≤16 years (39 pts aged 2–11); 54% of pts were male; 30 patients (44%) had acute lymphocytic leukemia. Chemotherapeutic agents received by ≥30% of pts were vincristine, cyclophosphamide, cytarabine, doxorubicin, methotrexate and PEG-L-asparaginase. Antibody-drug conjugates linked to ozogamicin were received by 3 and 1 pt, respectively.

Kaplan-Meier estimated day +100 survival was 77.4% (95% confidence interval, 65.4%–85.7%). For pts with vs without MOD, Kaplan-Meier estimated day +100 survival rates were 74.3% (56.4%–85.7%) vs 80.9% (62.3%–90.9%), respectively. At least 1 AE was reported in 44 pts (63.8%); 14 (20.3%) had AEs assessed by the investigator as at least possibly DF-related. Treatment-related AEs in ≥2 patients were hypertension (4.3%), nausea (2.9%), vomiting (2.9%), and epistaxis (2.9%). Hemorrhagic AEs of any severity occurring in ≥2 patients were pulmonary (7.2%), epistaxis (5.8%), and gastric (2.9%). Serious AEs were reported in 26 pts (37.7%), most commonly multi-organ failure (7.2%). AEs led to discontinuation in 4 pts (gastric, gastrointestinal and mouth hemorrhages, epistaxis, hypotension). No treatment-related deaths were reported.

**Conclusions:** Kaplan-Meier estimated Day+100 survival (77.4%) in pts developing VOD/SOS following various CT regimens without HSCT (80% pediatric, primarily children) is an encouraging finding. DF treatment in this group of 69 pts developing VOD/SOS post-CT was well-tolerated, with only 5.8% of pts discontinuing due to an AE and no treatment-related fatalities.

**Support:** Jazz Pharmaceuticals

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Pooled Treatment Analysis of Pediatric Patients with Defibrotide for Hepatic Veno-Occlusive Disease/ Sinusoidal Obstruction Syndrome and Multi-Organ Dysfunction Following Hematopoietic Stem Cell Transplant

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**Introduction:** Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) can be a life-threatening complication of stem cell transplant (SCT) conditioning regimens. Severe hepatic VOD/SOS, with multi-organ dysfunction (MOD), may be associated with >80% mortality. Defibrotide (DF) is approved for severe hepatic VOD/SOS treatment in the European Union. DF is available via an ongoing expanded-access protocol in the United States.

**Methods:** DF treatment for hepatic VOD/SOS with MOD is being assessed in patients (pts) from 3 clinical programs: a phase 2 dose-finding trial, a pivotal phase 3 study comparing DF to historical controls (HC), and a single-arm expanded-access program. Pts were randomized to receive 25 or 40 mg/kg/day in the dose-finding study; treated pts received 25 mg/kg/d in the other 2 studies. DF was given in 4 divided doses for a recommended ≥14 days (dose-finding) or ≥21 days (pivotal, expanded-access). VOD/SOS was defined by Baltimore and/or modified Seattle criteria. We report results for DF treatment 25 mg/kg/day in the subset of pts aged ≤16y with VOD/SOS and MOD post-SCT across these 3 studies.

**Results:** 255 pts received DF 25 mg/kg/d (dose-finding, n=22; pivotal, n=44; expanded-access, n=189); 29.8%...
Transplantation, National Cancer Center Hospital, Tokyo, Takuya Yamashita, Ryuji Tanosaki, Kensei Tobinai, HCT is less apparent. To evaluate the patient-host disease and other late effects, its role after autologous allogeneic HCT that may predispose patients to graft-versus-complications and patient education. While the importance of these effects in order to maintain patients after hematopoietic cell transplantation (HCT), more attention is needed.

Background: Cross-Sectional Patient Survey on the Need for a LTFU program after autologous HCT as well as the nature of self-administered questionnaires, these results would help to construct a LTFU program after autologous HCT.

Results: Among 231 patients who received autologous HCT, 114 were alive free of relapse. The questionnaires were mailed to 71 patients who had visits to our clinic, and 43 (61%) responded. Male accounted for 51%; the median duration after HCT was 4 years (1-19 years), and the median age at survey was 59 years (32-73). Twenty-one patients (56%) reported 44 disorders diagnosed after discharge (the median time of onset, 11 years from HCT, range, 0.1-8.9 years). Infection was the most frequent episode (n=19) and VZV accounted for 11 of them. Chronic renal failure (n=4) and endocrine disorders (n=4) were also documented. To the questions regarding “daily life” and “physical condition” after discharge, 24 (63%) and 35 (81%) patients, respectively, answered that they had experienced troubles. To the question asking the need for a LTFU program after autologous HCT, 39 patients (91%) answered “Yes”. As the role of the LTFU clinic, they wished to get information on daily life including food and exercise, to learn how to cope with specific symptoms, and to learn how similar patients were doing.

Conclusions: More than 80% of the participants answered that they had experienced disorders or troubles other than the primary disease after discharge, and 91% of participants suggested the need for a LTFU program after autologous HCT. Although we must acknowledge the potential selection bias including food and exercise, to learn how to cope with specific symptoms, and to learn how similar patients were doing.

Support: Jazz Pharmaceuticals

Cross-Sectional Patient Survey on the Need for a Long-Term Follow-Up Program after Autologous Hematopoietic Cell Transplantation

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Background: With a growing number of long-term survivors after hematopoietic cell transplantation (HCT), more attention has been paid to monitor and prevent late adverse effects in order to maintain patients’ quality of life. The long-term follow-up (LTFU) program plays a role in screening of complications and patient education. While the importance of the LTFU program has been increasingly recognized after allogeneic HCT that may predispose patients to graft-versus-host disease and other late effects, its role after autologous HCT is less apparent. To evaluate the patient’s need for a LTFU program after autologous HCT as well as the incidence of late effects, we conducted a single-center cross-sectional questionnaire survey.

Methods: We included adult patients who received autologous HCT for hematological malignancy at our center from January 1993 to February 2014, stayed free of relapse and are making regular visits to our clinic. Questionnaires were designed to ask about complications/disorders (diagnosis, year of diagnosis, occasion of diagnosis and treatment), annoying symptoms or troubles they experienced after discharge, thoughts and expectations on LTFU clinic, and social background (marital status, employment, and conception/conception). The patient background was extracted from the transplant registry database.

Results: Among 231 patients who received autologous HCT, 114 were alive free of relapse. The questionnaires were mailed to 71 patients who had visits to our clinic, and 43 (61%) responded. Male accounted for 51%; the median duration after HCT was 4 years (1-19 years), and the median age at survey was 59 years (32-73). Twenty-one patients (56%) reported 44 disorders diagnosed after discharge (the median time of onset, 11 years from HCT, range, 0.1-8.9 years). Infection was the most frequent episode (n=19) and VZV accounted for 11 of them. Chronic renal failure (n=4) and endocrine disorders (n=4) were also documented. To the questions regarding “daily life” and “physical condition” after discharge, 24 (63%) and 35 (81%) patients, respectively, answered that they had experienced troubles. To the question asking the need for a LTFU program after autologous HCT, 39 patients (91%) answered “Yes”. As the role of the LTFU clinic, they wished to get information on daily life including food and exercise, to learn how to cope with specific symptoms, and to learn how similar patients were doing.

Conclusions: More than 80% of the participants answered that they had experienced disorders or troubles other than the primary disease after discharge, and 91% of participants suggested the need for a LTFU program after autologous HCT. Although we must acknowledge the potential selection bias including food and exercise, to learn how to cope with specific symptoms, and to learn how similar patients were doing.

Support: Jazz Pharmaceuticals

Secondary SOLID Tumors after Allogeneic STEM CELL Transplantation: A CROSS-SECTIONAL Evaluation in 260 Adults at 1-Year Follow-up

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Introduction: Allogeneic hematopoietic cell transplantation (HCT) is an effective therapeutic option for high-risk hematological malignancies; 80% of those who survive the first 2-years are expected to become long-term survivors. The prevalence of chronic health conditions approaches 75% among HCT survivors and that for severe or life-