SUPPLEMENTARY APPENDIX

Predicting sinusoidal obstruction syndrome after allogeneic stem cell transplantation with the EASIX biomarker panel

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Supplementary methods

Methods

Study population

Patient, laboratory and clinical data were accessed retrospectively using the clinical data management software SAP and COPRA.

Definitions

EBMT criteria for SOS/VOD diagnosis in adults: These criteria differentiate between classical SOS/VOD, which occurs in the first 21 days after stem cell transplantation, and late-onset SOS/VOD, which occurs beyond 21 days after stem cell transplantation. Classical SOS/VOD diagnosis requires bilirubin levels to be ≥ 2 mg/dL and two of the following criteria to be present: painful hepatomegaly, weight gain > 5%, and ascites. Late onset SOS/VOD can be diagnosed if the classical criteria are met, SOS/VOD is histologically proven, or if hemodynamical or/and ultrasound evidence of SOS/VOD are present and at least two of the four EBMT criteria are met.

Statistical analyses

The primary objective was prediction of SOS/VOD occurrence. Primary analysis was performed for the binary endpoint “cumulative incidence of SOS/VOD within 28 days after alloSCT” and the time-to-event endpoint “time to VOD (TTV)” which is defined as time from alloSCT to diagnosis of SOS/VOD. Secondary objectives were the prediction of OS and time to NRM measured from the day of alloSCT. TTV respectively NRM were analyzed using competing event models. The competing events are “non-SOS/VOD-mortality” defined as time from alloSCT to death without prior SOS/VOD respectively time to relapse defined as time from alloSCT to relapse of disease.

Categorical variables are presented as numbers and percentages. Continuous variables are presented as medians and ranges or interquartile ranges (IQR). For the primary statistical

analysis of EASIX-d0, the log2 transformed index, log2(EASIX) = log2(LDH) + log2(creatinine) – log2 (thrombocytes) was used.

Median follow-up time was estimated using the reverse Kaplan-Meier method. The analyses of the binary endpoint SOS/VOD within 100 days after alloSCT were performed using logistic regression models. We report estimated odds ratios (OR) and corresponding confidence intervals. The OR is the ratio of the estimated odds for a SOS/VOD event given a defined risk factor and the odds for a SOS/VOD event in the absence of this risk factor. Survival and incidence curves are based on the Kaplan-Meier estimator respectively Aalen-Johanson estimator for competing risk scenarios. For univariable and multivariable analyses of OS and NRM, (cause-specific) Cox proportional hazards models were used. Hazard ratios (HR) were calculated to demonstrate the prognostic effect of biomarkers. To check whether EASIX-d0 improves individual risk prediction in the presence of the well-established CIBMTR score, we trained a multivariable model with log2(EASIX) and the individual risk prediction from the CIBMTR calculator as covariates.

Validation of univariate EASIX-d0 and CIBMTR SOS/VOD model (Berlin) was performed in an external validation cohort (Heidelberg, no pravastatin/UDA). Discriminative ability was assessed using ROC-curves and AUC. Additionally, the Brier score was included which is a function measuring the accuracy of predictions. In contrast to the c-index, the Brier score checks for both, discrimination as well as calibration of the model. If the Brier score of a statistical model (including EASIX) is lower than the Brier score of the null model (without EASIX), a better prediction (of SOS/VOD) is indicated.

Pravastatin and UDA were routinely applied in the Heidelberg cohort starting in 01/2010, whereas the training cohort did not regularly receive pravastatin and UDA as prophylaxis. To assess differences in the prognostic effect of EASIX-d0 between subgroups of patients with pravastatin/UDA prophylaxis or no pravastatin/UDA prophylaxis, separate subset Cox regression models for the Heidelberg cohort were performed (Heidelberg no pravastatin/UDA vs Heidelberg with pravastatin/UDA). Estimates based on the univariate logistic training

cohort model can be obtained via an online calculator which is available on http://biostatistics.dkfz.de/EASIX/. The tool provides an estimate of the probability for SOS/VOD within 28 days after alloSCT and a corresponding confidence interval given a certain EASIX-d0 value.