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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndromes (MDS)

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Purpose. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for patients with myelodysplastic syndromes (MDS). Several issues must be considered when evaluating the benefits and risks of HSCT for patients with MDS, with the timing of transplantation during the disease course being a crucial question.
Recently the integration of genomic screening (by Molecular International Prognostic Scoring System, IPSS-M) into patient's assessment has resulted into a significant improvement in predicting clinical outcomes with respect to the conventional prognostic score (Revised IPSS, IPSS-R), including better stratification of post-HSCT outcome.
Here, we aimed to develop and validate a Decision Support System to define the optimal timing of HSCT in MDS patients based on clinical and genomic information as provided by IPSS-M vs conventional IPSS-R.
Patients and methods. We studied a retrospective, international cohort of 8,326 patients with MDS for whom complete set of clinical and molecular information was available. Patients were stratified into a learning and validation cohorts (65%, n=5411 vs. 35%, n=2915). The decision-strategy analysis was divided into two parts. First, we developed a multi-state model to estimate transition hazards between different disease strata. Age and IPSS-R/IPSS-M were used as explanatory variables. The time elapsed between the diagnosis of MDS and HSCT was also considered as covariate in the models, which were further adjusted for disease-modifying therapy (if any). Next, we developed a Semi-Markov multi-state decision model based on microsimulation to compare various transplantation strategies according to the timing of the procedure, conditionally on covariates of interest. The microsimulation strategy simulates a hypothetical randomized clinical trial where subjects are randomized to receive HSCT at different time points. Results were used to estimate the average survival time over an 8-year time horizon (Restricted Mean Survival Time, RMST) for each combination of covariates, and then determine the optimal transplantation policy by compared the different strategies.
Results. When considering patient life expectancy for patients who received a HSCT (Restricted Mean Survival Time, RMST) in the learning cohort, in both scenarios of IPSS-R and IPSS-M based transplantation policies, early disease stage was associated with a better clinical outcome. Indeed, life expectancy after transplantation was higher for younger vs elderly patients (*Figure 1 and 2*). Under an IPSS-R based policy, patients with low-risk disease clearly benefit from a delayed transplantation policy across all age groups, while in patients belonging to intermediate, high/very high risk categories immediate transplantation was associated with a prolonged life expectancy, regardless of age. (*Figure 1*) Considering an IPSS-M based policy, patients with either low and moderate-low risk benefit from a delayed transplantation policy (across all age groups), while in those belonging to moderate-high, high and very high risk categories immediate transplantation was associated with a prolonged life expectancy (across all age groups, *Figure 2*). Importantly, all these results were confirmed in the validation cohort, thus providing evidence for their reliability and generalizability.
Modelling decision analysis on IPSS-M vs. original IPSS-R changed transplantation policy in a significant proportion of patients, resulting in a gain-in-life expectancy under an IPSS-M based policy across all age groups ($P<0.001$). Specifically, 19% of candidates to be immediately transplanted under an IPSS-R based policy would benefit from a delayed strategy under an

IPSS-M based policy, while 21% of candidates to delayed transplantation under an IPSS-R based policy, would benefit from immediate HSCT under an IPSS-M based policy.
We have created a prototype web application for the MDS Transplantation Decision Support System, that allows clinicians to define the best timing for HSCT starting from individual patient demographics, IPSS-R, and IPSS-M information.
Conclusion. We provided evidence for the clinical relevance of including genomic features into the transplantation decision making process, specifically regarding the optimal timing of HSCT, allowing personalizing of the hazards and effectiveness of HSCT in patients with MDS.

Disclosures Meggendorfer: *MLL Munich Leukemia Laboratory:* Current Employment. **Voso:** *Jazz:* Other: Advisory Board; *Celgene/BMS:* Other: Advisory Board; *Astra Zeneca:* Speakers Bureau; *Novartis:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Jazz:* Speakers Bureau; *Astellas:* Speakers Bureau; *Novartis:* Research Funding; *Celgene/BMS:* Research Funding, Speakers Bureau; *Syros:* Other: Advisory Board. **Díaz-Beyá:** *Bristol Myers Squibb:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Jazz Pharma:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria. **Rambaldi:** *Abbvie:* Honoraria. **Passamonti:** *Novartis, GSK, Bristol Myers Squibb, Celgene, Sierra Oncology, AbbVie, Janssen, Roche, AOP Orphan, Karyopharm, Kyowa Kirin, MEI, Sumitomo:* Honoraria; *Roche:* Consultancy; *Abbvie:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Research Funding. **Ciceri:** *ExCellThera:* Other: Scientific Advisory Board . **Santoro:** *Gilead:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; 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Figure 1. Optimal timing of transplantation in the learning cohort, according to a IPSS-R based-policy. The decision model based on microsimulation simulated a hypothetical randomized clinical trial where subjects are randomized to receive HSCT at different time points upon disease diagnosis. Results were used to estimate the average survival time over an 8-year time horizon (Restricted Mean Survival Time, RMST), for each combination of covariates. RMST estimates were compared among different transplantation policies thus determining the optimal transplantation policy.

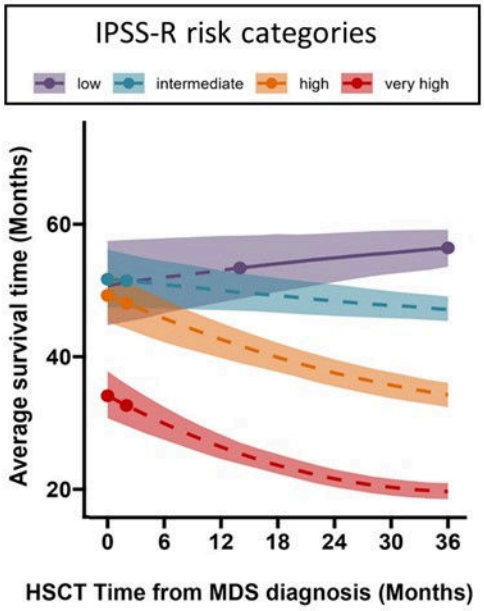

Figure 2. Optimal timing of transplantation in the learning cohort, according to a IPSS-M based-policy.

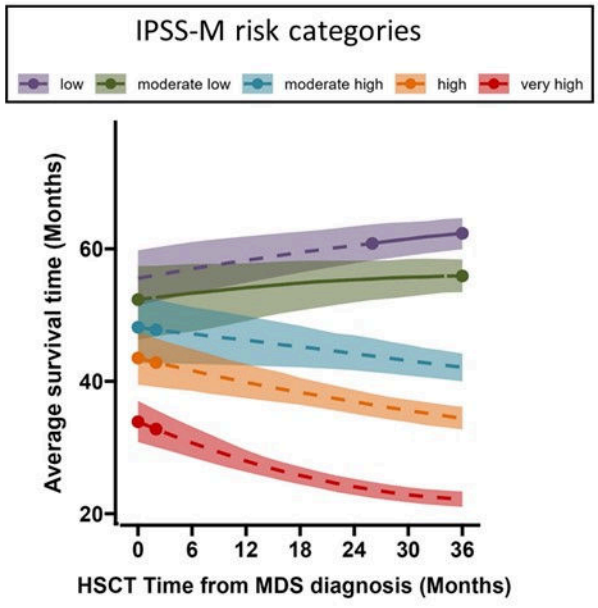

Figure 1

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