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Source / Izvornik: **Bone Marrow Transplantation, 2021, 56, 3084 - 3087**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1038/s41409-021-01458-9

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:593052

Influence of Pre-Transplant Inflammatory Bowel Disease on the Outcome of Allogeneic Hematopoietic Stem Cell Transplantation: A Matched-Pair Analysis Study from the Transplant Complications Working Party (TCWP) of the EBMT

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The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been constantly increasing with the introduction of reduced-intensity conditioning (RIC) and alternative types of cell sources and donors. However, non-relapse-mortality (NRM), related mainly to graft-versus-host disease (GVHD), remains the major limitation for allo-HSCT, making its estimates important when considering this therapeutic approach. The most frequently used tool for making this prediction in clinical practice is the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI).[1] HCT-CI integrates 17 relevant pre-transplant organ-specific comorbidities, among which is inflammatory bowel disease (IBD), comprised of Crohn's disease and ulcerative colitis. The inclusion of IBD in HCT-CI is based on a Cox regression risk model which identified its association with increased NRM (Hazard ratio (HR), 1.3) and grade III-IV acute GVHD (HR, 1.6).[1,2] However, the only available formal analysis of NRM and GVHD risk in patients with IBD compared to matched controls failed to show any significant difference between the groups.[3]

We therefore used the European Society for Blood and Marrow Transplantation (EBMT) dataset and designed a case-controlled analysis with the aim of assessing the outcomes of allo-HSCT in hematologic patients with and without prior IBD. The study included all EBMT registry patients age >=18 years with known IBD who underwent a sibling or unrelated allo-HSCT between 2011 and 2015 for a hematologic malignancy. Patients with IBD were matched with 3 controls without any record of IBD before transplant, according to patient age, disease risk, intensity of conditioning, donor type and HLA disparity, Karnofsky score and GVHD prophylaxis. Cumulative incidence (CI) estimates of acute GVHD, chronic GVHD, relapse, and NRM were calculated with relapse or death from other causes defined as competitive events, using the Gray test for univariate analysis. Probabilities of overall survival (OS) and GVHD-free-relapse-free-survival (GRFS) were estimated using the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. Multivariate analyses were performed using the Cox proportional-hazard model. In order to take into account correlation between cases and their controls, the multivariate Cox models included a cluster term for each quadruplet. Factors known to influence the outcomes were also included in the model: patient gender and year of transplantation.

Between 2011 and 2015, 174 patients with IBD who underwent allo-HSCT for a hematologic malignancy were reported to EBMT. Of these, 163 could be paired with 3 controls and were therefore included in the study (the 11 remaining patients did not have a match). The analyzed IBD cohort comprised 90 males and 73 females, with a median age of 55 years (range 18- 79). The most frequent malignancies in the IBD group were acute leukemia (n=98; 60%) and myelodysplastic/myeloproliferative neoplasm (n=40; 25%). The donor was an identical sibling for 60 patients (37%) and an unrelated donor for 103 patients (63%).

Seventy-six patients (47%) received a myeloablative conditioning regimen while 87 patients (53%) received RIC. In the IBD group, 154 patients (94%) received peripheral blood stem cells, while 9 patients (6%) received bone marrow. Baseline characteristics of cases and controls were well matched as shown in ***Table 1***.

With a median follow-up of 49 months for the patients with IBD and 52 months for controls, the CI of NRM at 36 months was 24% (95% CI, 17-31) for patients with IBD and 29% (95% CI, 24-33) for controls (HR, 0.86; 95% CI, 0.59-1.26; p=0.45) (***Figure 1A***). The CI of grade II-IV acute GVHD at 100 days was 31% (95% CI, 23-39) for patients with IBD and 29% (95% CI, 25-34) for controls (HR, 1.09, 95% CI, 0.77-1.54, p=0.64) (***Figure 1B***). The CI of chronic GVHD at 36 months was 44% (95%CI, 36-52) in patients with IBD and 37% (95% CI, 32-42) in controls (HR, 1.37; 95% CI, 1.03 to 1.81; p=0.03) (***Figure 1C***). The relapse incidence at 36 months was 36% (95% CI, 28-44) in patients with IBD and 31% (95% CI, 27-36) in controls (HR, 1.24; 95% CI, 0.90-1.71; p=0.19) (***Figure 1D***). OS at 36 months was 47% (95% CI, 39-56) for patients with IBD and 47% (95% CI, 42-52) for matched controls (HR, 1.00; 95% CI, 0.78-1.28; p=0.99) (***Figure 1E***). Finally, GRFS at 36 months was 24% (95% CI, 18-32) for patients with IBD and 30% (95% CI, 26-35) for controls (HR, 1.15; 95% CI, 0.95-1.39; p=0.16) (***Figure 1F***).

Contrary to our expectations, but similarly to the previous French study, we found no difference in terms of NRM or acute GVHD between patients with and without IBD (3). On the other hand, and in opposite to the French study, we found significantly more chronic GVHD in IBD patients compared to controls. However, we performed the largest case-controlled analysis of allo-HSCT in 163 hematologic patients with IBD, while the French study included only 18 IBD patients. The hypothesis that patients with IBD might have more acute GVHD arises from the fact that GVHD and IBD seem to share same genetic associations, immunological characteristics and possibly even driving mechanisms (4). Namely, it has been recognized that intestinal barrier dysfunction and alterations in the gut microbiome play a key role in the initiation of both diseases (5,6). It is much harder to speculate on the potential association between chronic GVHD and IBD. Nevertheless, the loss of barrier function and gut dysbiosis also seem to impact the onset of many different autoimmune diseases as well as GVHD in non-intestinal target organs (7).

Allo-HSCT has been performed not only for standard hematologic indications in patients with IBD, but also specifically for the treatment of refractory IBD, with promising results (8). However, due to the higher NRM associated with allo-HSCT, autologous HSCT (auto-HSCT) has been performed in resistant IBD more frequently, although with variable responses (9). The rationale of auto-HSCT is to eliminate self-reactive lymphocytes with lymphoablative chemotherapy, allowing the generation of new self-tolerant

lymphocytes. Theoretically, allo-HSCT could also overcome genetic predisposition to IBD, while the resulting GVHD could eliminate self-reactive lymphocytes that might survive conditioning. However, due to the perceived risk/benefit ratio and limited data in the allo-HSCT setting, auto-HSCT is currently preferred in patients with severe IBD resistant to other treatments. Moreover, auto-HSCT is currently being evaluated for the treatment of refractory Crohn's disease in a phase III multicentric randomized trial in comparison to standard care (10).

Unfortunately, the retrospective nature of our study precluded the analysis of the response of IBD to allo-HSCT. It would be worthwhile to track this information in future studies, as this might add valuable data on the potential therapeutic effect of allo-HSCT in IBD. The limitation of our analysis is also the fact that we were not able to evaluate the status of IBD before allo-HSCT, since it is likely that this could impact both the development of GVHD and the recurrence of IBD post allo-HSCT. In conclusion, our results suggest that IBD should not be considered a contraindication for allo-HSCT in patients with hematologic diseases; and its impact on the comorbidity index should be reduced. However, although hematologic patients with previous IBD do not appear to be at higher risk of acute GVHD after allo-HSCT, they might have a higher probability of developing chronic GVHD, which could considerably impair their long-term quality of life.

Acknowledgements: Not applicable.

Financial disclosure: There are no financial disclosures to report.

Conflict of interest statement: The authors have no conflicts of interests to report.

Authors' contributions: Z.P. assembled and analyzed data and wrote the first version of the manuscript. C.K., H.S., O.P. and G.B. designed the study, supervised research, analyzed data, and helped with writing the manuscript. E.P. and C.P. assembled the data, performed statistical analysis and commented on the manuscript. All other co-authors collected data, recruited patients and helped with writing the manuscript. All authors approved submission of the manuscript for publication.

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Figure 1.

Cumulative incidence of NRM at 36 months (1A), 24% (95% CI, 17-31) in patients with IBD and 29% (95% CI, 24-33) in patients without IBD, p=NS

Cumulative incidence of grade II-IV acute GVHD at 100 days (1B), 31% (95% CI, 23-39) in patients with IBD and 29% (95% CI, 25-34) in patients without IBD, p=NS

Cumulative incidence of chronic GVHD at 36 months (1C), 44% (95%CI, 36-52) in patients with IBD and 37% (95% CI, 32-42) in patients without IBD, p=0.03

Cumulative incidence of relapse at 36 months (1D), 36% (95% CI, 28-44) in patients with IBD and 31% (95% CI, 27-36) in patients without IBD, p=NS

Overall survival at 36 months (1E), 47% (95% CI, 39-56) in patients with IBD and 47% (95% CI, 42-52) in patients without IBD, p=NS

GVHD-free-relapse-free survival at 36 months (1F), 24% (95% CI, 18-32) in patients with IBD and 30% (95% CI, 26-35) in patients without IBD, p=NS

dashed line-patients without pre-HSCT IBD, solid line-patients with pre-HSCT IBD.