Check for updates

ELSEVIER

Blood 142 (2023) 3557–3558

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Prednisolone Intake Differentially Regulates IL12p40 and IL18 - Impact on Severe Chronic Gvhd, Relapse and Mortality

Salim Oulghazi, MD[1], Leonard Petry[2], Mark E Robinson, PhD[3], Richard Huth[4], Caroline Pabst[5], Peter Dreger, MD[6], Thomas Luft, MDPhD[7]

[1] Center of Molecular and Cellular Oncology, Yale University, New Haven, CT
[2] University Hospital Heidelberg, Heidelberg, Germany
[3] Yale University, Boston, CT
[4] Department of Medicine V, Hematology, Oncology and Rheumatology, University Hosp, Heidelberg, DEU
[5] University Hospital Heidleberg, Heidelberg, DEU
[6] Universitätsklinikum, Heidelberg, Germany
[7] University of Heidelberg, Heidelberg, Germany

Background: Chronic graft-versus-host disease (cGVHD) is an immune-mediated complication after allogeneic stem cell transplantation (alloSCT). It is associated with graft-versus-leukemia effects and lower relapse rates, but in its severe form also with increased morbidity and mortality. The early interferon-gamma (IFNγ)-response marker CXCL9 is increased in mild and severe cGVHD and strongly correlates with IDO activity (1). Interleukin (IL)-18 is an innate, IFNγ inducing cytokine that associates with poor outcome of allografted patients (2), and with severe fibrosing cGVHD (1). The adaptive immunological arm of IFNγ induction relies on IL12 that is produced during cognate interactions between dendritic cells and T cells. IL12 kinetics is poorly characterized after alloSCT.
We hypothesized that adaptive (IL12p40) and innate (IL18) immune mediators and their modulation by immunosuppressive drugs (ATG, prednisolone) impact cGVHD severity and outcome.
Methods: Patients before alloSCT were included in an observational study allowing collection of clinical data and blood before and for one year after alloSCT. The training cohort included 350 patients transplanted before 2018 at our institution. The validation cohort consisted of 205 patients transplanted after 2018. Patients were eligible if they were not relapsed and did not receive donor leukocyte infusions (DLI) until d180, and did not develop refractory acute GVHD.
Cytokines that belonged to the IFNγ pathway (IFNγ, CXCL9, CXCL10, IL12p40, IL12EBI3, IL17, IL18, IL23) or to innate inflammatory pathways (TNFa, IFNa, IL1b, activin, follistatin) were measured by R&D ELISAs. Cumulative (equivalent) prednisolone dosages between d0 and d100 after alloSCT were calculated from electronic patient records. Flow cytometry of PBMC of 100 patients on day+180/onset cGVHD were performed using 24-gate multicolor staining. Mild, severe fibrosing and severe gastro-intestinal (GI) cGVHD were diagnosed according to simplified NIH criteria (training cohort only). Overall survival, non-relapse mortality and time to relapse from time of blood sampling were calculated by multivariable Cox regression analyses.
Results: Median time of blood sampling at onset of cGVHD (n=180) was day +168 (range 41-723). Control patients (n=169) were collected on day +180 (171-183). Mild cGVHD was recorded in 133 patients, severe fibrosing cGVHD in 39 patients, and isolated GI-cGVHD in 8 patients.
Receiver-operator characteristic (ROC) curves showed that only CXCL9, IL18 and IL12p40 were significantly linked to severe cGVHD. IL18 was associated with severe fibrosing cGVHD, whereas CXCL9 and IL12p40 were correlated to any grade cGVHD. In multivariable Cox analyses including IL12p40, IL18, age, mismatch, recipient and donor gender, disease stage, ATG, MTX, and diagnosis, IL18 associated with poor OS (HR per log2 increase 1.81 (1.19-2.74, p=0.005), whereas IL12p40 associated with superior OS (HR 0.53 (0.35-0.81), p=0.003). This could be validated in the independent cohort.
Time course analyses of serum levels of CXCL9, IL12p40 and IL18 revealed a strong increase of CXCL9 and IL12p40 toward onset of cGVHD, but no stimulation of IL18 levels. Cumulative prednisolone intake>100 mg until day+100 significantly reduced IL12p40 serum levels on d180/at onset of cGVHD, without influencing IL18 production (Figure 1). In contrast, ATG reduced both, IL18 and IL12p40 at day180/onset of cGVHD. This might explain the reduced incidence of severe fibrosing cGVHD in patients receiving ATG prophylaxis (days-3 to -1 before alloSCT, 4% vs. 23%, p<0.001, n=343), whereas no effect of early prednisolone intake was noticed (p=0.916, n=137).

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/3557/2204848/blood-159-main.pdf by guest on 12 June 2024

© 2023 by The American Society of Hematology

Multicolor flow cytometry showed that IL12p40, but not IL18 correlated with blood counts of T-lymphocyte populations, including CD4+, CD8+ and $\gamma\delta$-Tcells. IL12p40 and $\gamma\delta$-Tcells were associated with reduced relapse rates.
In summary, CXCL9, IL12p40 and IL18 are associated with severe cGVHD. IL18 correlated with severe fibrosing cGVHD and increased mortality, whereas IL12p40 was associated with reduced NRM, reduced relapse risk, improved lymphocyte recovery and $\gamma\delta$-T-cells, and was affected by prednisolone intake but not ATG.
Conclusion: These results may help to understand and potentially separate the GVL effects from mortality/morbidity that associate with cGVHD.
1)PMID34755129 2)PMID31680001

Disclosures Dreger: *Riemser:* Consultancy, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Speakers Bureau; *BMS:* Consultancy, Honoraria; *Gilead:* Consultancy, Speakers Bureau; *Beigene:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Roche:* Consultancy, Speakers Bureau; *Miltenyi:* Consultancy.

Figure 1: Prednisolone intake between day0 and day100 after alloSCT reduces IL12p40 at onset of cGVHD without affecting IL18.
N=62 patients at onset of cGVHD. p: Kruskal-Wallis test.

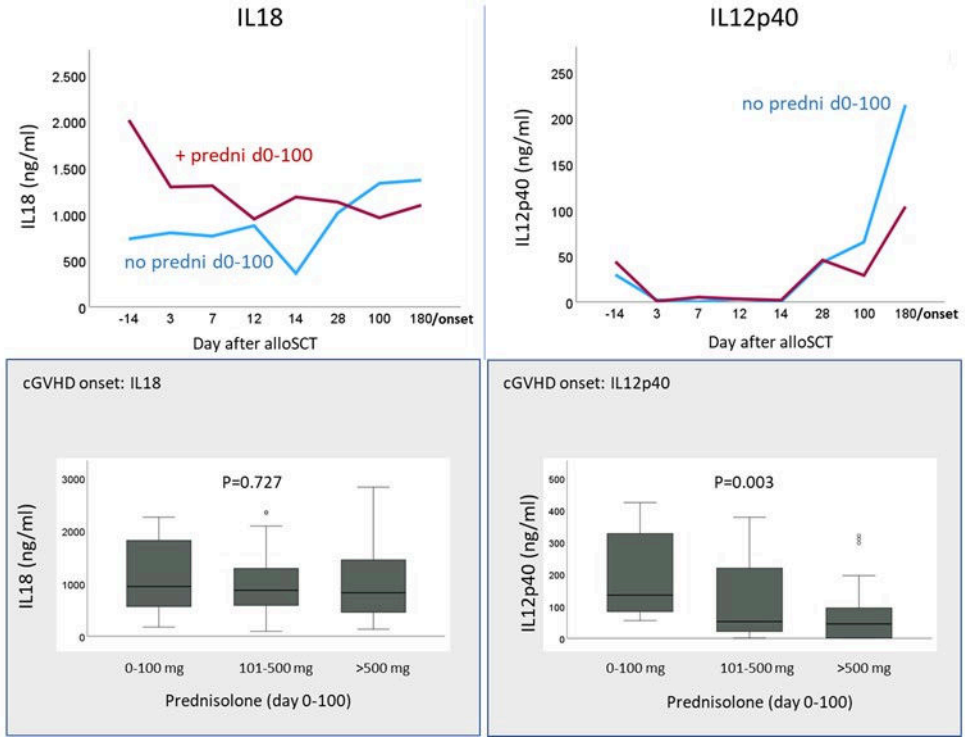

Figure 1

https://doi.org/10.1182/blood-2023-180784

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/3557/2204848/blood-159-main.pdf by guest on 12 June 2024