were treated from day 14 to day 28. Animals were assessed for acute GVHD clinically and by organ pathology. Curcumin effects on in vitro T cell proliferation and cytokine production were assessed u*in vitro*T cell activation assay using CD3/CD28 stimulation and in mixed lymphocyte reaction (MLR).
Results: Both preventive and therapeutic administration of curcumin resulted in improved survival on day +100 after alloHCT (50.5% vs 20% and 45% vs 20%, respectively). Curcumin attenuated GVHD by significantly suppressing serum levels of IL-6 and TNF-α along with significant reduction in gut pathology and concurrent induction of splenic Tregs on day +7 after alloHCT. T cell proliferative responses were suppressed in the presence of curcumin and a significant reduction in cytokine concentration, pSTAT3 and NFkB in the supernatant was observed.
Conclusions: Our data supports a beneficial effect of curcumin in the multifactorial pathogenesis of GVHD. Preventive curcumin treatment improved GI tract and clinical GVHD and survival, as well as therapeutic curcumin improved clinical GVHD and survival. Clinical relevance of curcumin is commonly questioned, as curcumin is known for often unsatisfactory bioavailability due to fast metabolism and degradation, as well as it has a multitude of effects. Nevertheless, it's positive safety profile and low toxicity risk make curcumin an attractive mother compound to prevent or treat GVHD, and its application in this field may be optimized by discovery of novel derivatives interfering with individual specific targets and improvement of pharmacokinetic properties, both of which are currently being tested in our lab.

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What Is the Outcome of Patients with Acute Leukemia Who Survive Severe Acute Graft-Versus-Host Disease?

Olle Ringden [1], *Myriam Labopin* [2], *Audry Mailhol* [3], *Dietrich W. Beelen* [4], *Behnam Sadeghi* [5], *Yngvar Floisand* [6], *Ardeshir Ghavamzadeh* [7], *Jürgen Finke* [8], *Gerhard Ehninger* [9], *Liisa Volin* [10], *Arnold Ganser* [11], *Christoph Schmid* [12], *Sebastian Giebel* [13], *Arnon Nagler* [14]. [1] *Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden;* [2] *Hopital Saint-Antoine, Paris, France;* [3] *Acute leukemia working party of EBMT, Paris, France;* [4] *University Hospital of Essen, Essen, Germany;* [5] *Division of Therapeutic Immunology, F79, Karolinska Institutet, Stockholm, Sweden;* [6] *Hematol, Oslo, Norway;* [7] *Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran (Islamic Republic of);* [8] *Department of Medicine, Haematology & Oncology, Freiburg University Medical Center, Freiburg, Germany;* [9] *Universitaetsklinikum Dresden, Dresden, Germany;* [10] *Third Department of Medicine, Stem Cell Transplantation Unit, HUCH Comprehensive Cancer Center, Helsinki, Finland;* [11] *Department of Hematology/Oncology, Medizinische Hochschule Hannover, Hannover, Germany;* [12] *Department of Hematology and Oncology, Klinikum Augsburg, Ludwig-Maximilians-University, Munich, Germany;* [13] *Department of Bone Marrow Transplantation and Oncohematology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland;* [14] *The Bone Marrow Transplantation Department, Division of Internal Medicine, The Chaim Sheba Medical Center, Tel-Hashomer, Israel*

Acute graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT). With new promising therapies, survival may improve in patients with severe acute GVHD. We wanted to analyze the long-term outcome among patients who survive severe acute GVHD.
Patients and Methods: This is a landmark analysis of 23,567 patients with acute leukemia who survived >6 months after HSCT during 2002-2014. Patients with severe acute GVHD (n = 1,738) were compared to controls.
Results: Patients with severe acute GVHD had a higher non-relapse mortality (NRM) and chronic GVHD compared to controls ($p < 10^{-5}$). Extensive chronic GVHD was 26.9% before 6 months and 27.2% after 6 months in the severe acute GVHD group ($p < 10^{-5}$). The probability of relapse was significantly lower in the severe acute GVHD group, and leukemia-free survival (LFS) and survival was significantly lower than for the controls ($p < 10^{-5}$). Five-year LFS in patients who survived severe acute GVHD was 49% as opposed to 61% in controls with no or mild, and 59% in patients with moderate GVHD.
Conclusion: HSCT patients who survive severe acute GVHD have a high risk of extensive chronic GVHD, a higher NRM, a lower relapse probability and lower LFS, compared to other HSCT patients.

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Selective Alloreactive Depletion Is Not a Mechanism Underlying the Efficacy of Post-Transplantation Cyclophosphamide in a Murine Haploidentical Transplantation Model

Lucas P. Wachsmuth [1], *Michael Eckhaus* [2], *Ehydel Castro* [1], *Ronald E. Gress* [1], *Christopher G. Kanakry* [1]. [1] *Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD;* [2] *Division of Veterinary Resources, Office of Research Services, Office of the Director, National Institutes of Health, Bethesda, MD*

Despite its clinical efficacy, the mechanisms by which post-transplantation cyclophosphamide (PTCy) prevents graft-versus-host disease (GVHD) remain poorly understood. The prevailing theory, extrapolated from murine skin allografting models, posits that PTCy preferentially eliminates alloreactive T cells, which may selectively proliferate early post-transplant. Those studies, which exploited strain-specific differential expression of certain T-cell receptor (TCR) Vβs as markers of alloreactive cells, also proposed two other mechanisms underlying PTCy's efficacy: intrathymic clonal deletion of alloreactive T cells and generation of suppressor T cells.
To test the hypothesis that PTCy works via preferential elimination of alloreactive T cells and investigate the biology of PTCy, we developed a murine model of haploidentical transplantation that more directly parallels clinical practice. In this model (B6C3F1→B6D2F1), the administration of 40×10^6 splenocytes and 10×10^6T-cell-depleted bone marrow cells following 10.5 Gy irradiation induces universally fatal GVHD, with the Vβ6 TCR serving as a marker of alloreactive T cells. Administration of PTCy on days +3 and +4 at doses ranging from 10 to 50 mg/kg effectively prevented lethal GVHD.
In untreated mice at day +7, the majority of T cells were proliferating as measured by Ki-67, consistent with recent human data. Mice treated with PTCy at ≥10 mg/kg had marked global reductions in Ki-67 + T cells, but this effect appeared non-selective. Indeed, Vβ6+ T cells (~6-12% of B6C3F1 T cells) persisted at normal frequencies at early (day +7 and +21) and late (day +200) timepoints post-transplant, inconsistent with selective alloreactive T-cell elimination or intrathymic clonal deletion. The latter was confirmed using thymectomized recipients, for which PTCy remained effec-