

What is the outcome of patients with acute leukemia who survive severe acute graft-versus-host disease?

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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 *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, its 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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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

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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) V β s 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 \rightarrow B6D2F1), the administration of 40 \times 10⁶ splenocytes and 10 \times 10⁶ T-cell-depleted bone marrow cells following 10.5 Gy irradiation induces universally fatal GVHD, with the V β 6 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 \geq 10 mg/kg had marked global reductions in Ki-67 + T cells, but this effect appeared non-selective. Indeed, V β 6+ 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 effective.