Graft-*versus*-host disease in allogeneic transplantation: the good and the bad

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doi:10.3324/haematol.2022.281425

TITLE	Antileukemic effect of graft-*versus*-host disease in human recipients of allogeneic-marrow grafts.
AUTHORS	Weiden PL, Flournoy N, Thomas ED, Prentice R, Fefer A, Buckner CD, Storb R.
JOURNAL	New England Journal of Medicine. 1979;300(19):1068-1073. PMID: 34792.

Now after more than 60 years of clinical research into allogeneic hematopoietic stem cell transplantation this treatment approach is well established as a curative option for many hematologic malignancies. One of the major complications of this treatment is an immunological-based complication which was initially named 'secondary disease' and is now well known as graft-*versus*-host disease (GvHD). The preclinical observation that GvHD in mice also resulted in eradication of leukemic cells was described by Mathe *et al.* as the graft-*versus*-leukemia effect.[1] Clinically, the powerful correlation between GvHD and an antileukemic effect in humans was convincingly demonstrated by Weiden and colleagues from Seattle in two seminal studies published in 1979 for acute GvHD and in 1981 for chronic GvHD.[2,3] Patients who experienced acute GvHD had a 2.5 times lower relative relapse rate than those without GvHD. Notably, during the first 130 days after allogeneic stem cell transplantation the relapse rate among patients with acute GvHD grade II to IV was ten times lower than that in patients without (grade 0 to I) GvHD and 13 times lower than that among syngeneic graft recipients (Figure 1).[2] Despite this lower incidence of relapse the benefit for overall survival was offset by a higher non-relapse mortality in patients with GvHD. This described clinical observation highlighted the double-edged sword of GvHD

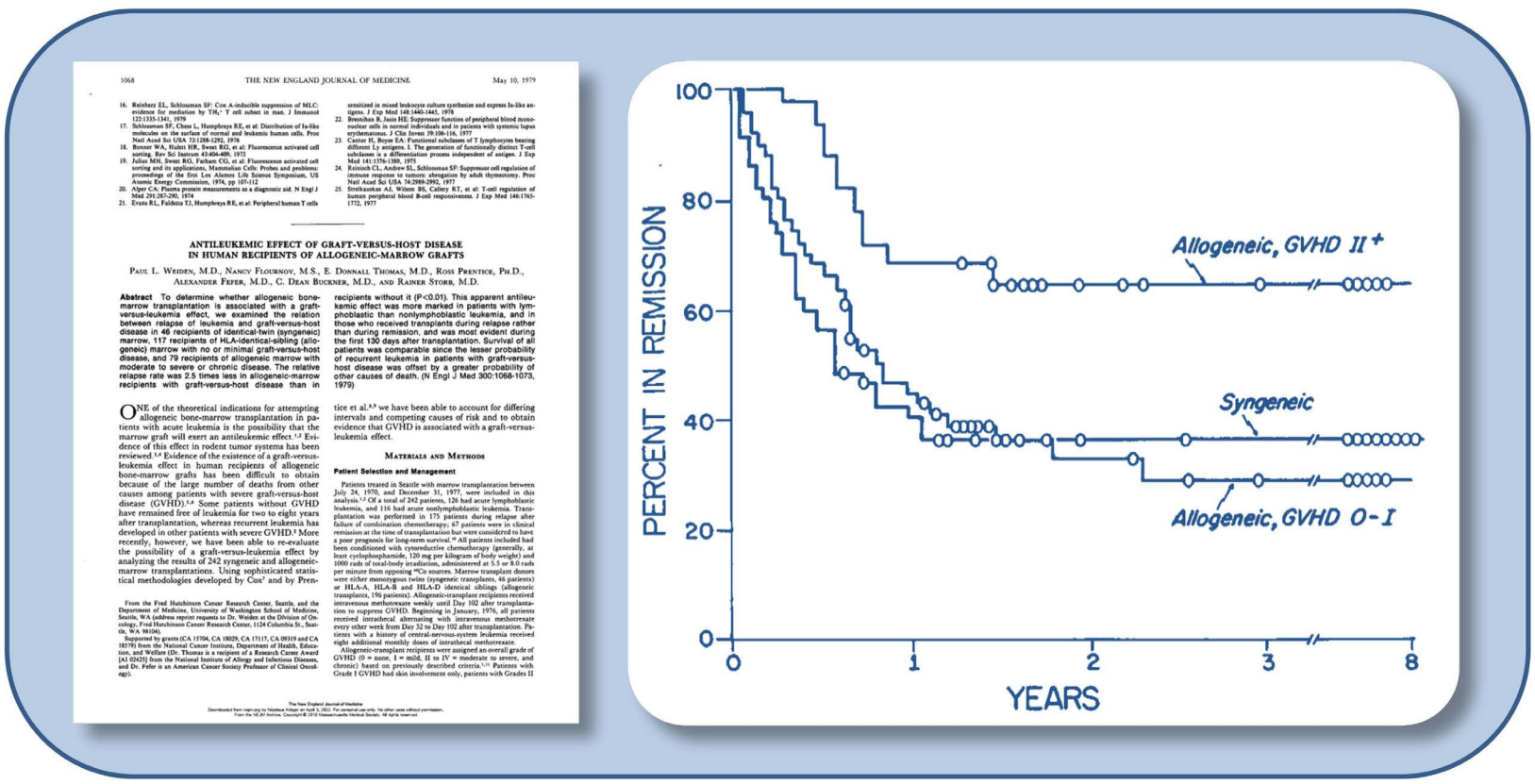

Figure 1. Kaplan-Meier probability of remaining in remission after allogeneic bone marrow transplantation for acute leukemia according to the occurrence of acute graft-*versus*-host disease. Figure drawn from Weiden *et al.* NEJM 1979.[2] GVHD: graft-*versus*-host disease.

regarding toxicity and cure and has boosted preclinical and clinical research in order to separate GvHD from the graft-*versus*-leukemia effect and to develop clinical strategies to reduce GvHD without inducing a higher rate of relapse. This work, which demonstrated the crucial effect of donor T cells in eliminating leukemia cells, was also the rationale for the use of donor T cells after transplantation (donor leukocyte infusion) to treat relapse in chronic myeloid leukemia and other diseases, resulting in impressive remission rates.[4] Later, multiple approaches to reduce the risk of GvHD without increasing the risk of relapse were investigated and were used in clinical practice. These approaches included antithymocyte globulin and selected depletion of α/β T cells, as well as an increased antileukemic effect with adoptive immunotherapy using leukemic-specific T cells, chimeric antigen receptor T cells or natural killer cells among others.

However, despite clinical improvement in reducing GvHD and harnessing the graft-*versus*-leukemia effect, initiated by Weiden's seminal paper, a clear separation between GvHD and the graft-*versus*-leukemia effect still remains, in 2022, the holy grail of allogeneic stem cell transplantation.[1-4]

Disclosures

No conflicts of interest to disclose.

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