Graft-*versus*-leukemia

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https://doi.org/10.3324/haematol.2025.287401

TITLE	Antileukemic effect of graft-*versus*-host disease in human recipients of allogeneic-marrow grafts.
AUTHORS	Weiden PL, Flournoy N, Thomas ED, *et al*.
JOURNAL	The New England Journal of Medicine. 1979;300(19):1068-1073. doi: 10.1056/NEJM197905103001902.

In 1979 an article published in *The New England Journal of Medicine* by Weiden *et al*., describing the graft-*versus*-leukemia (GvL) effect following allogeneic marrow transplantation, offered the first clear, consistent demonstration of the ability of the human immune system to eradicate cancer.[1] Specifically, the Seattle group found that relapse was far less common in patients who received allogeneic marrow and developed graft-*versus*-host disease (GvHD) than in those who had no GvHD or received syngeneic marrow (Figure 1). True, isolated anecdotal reports of tumor regression associated with infection had been published dating back 100 years to the time of William Cooley, but the 1979 article was the first to convincingly show the capability of the human immune system to eliminate a disseminated malignancy.

The demonstration of the GvL effect fueled an enormous amount of research into how to further harness the power of immunity, ultimately resulting in today's many immunotherapies including the most direct progeny of marrow transplantation, adoptive T-cell therapy. Once the GvL effect was recognized, physicians began treating patients for post-transplant relapse using infusion of viable donor lymphocytes, resulting in sustained remission in a few, but worsened GvHD in many. Increased potency and specificity were obviously needed.

By the 1980s, work in murine models had demonstrated that it was possible to identify, isolate, and expand tumor reactive T cells and use them to eradicate established tumors in mice. The question then was how to do this in humans. Using cytomegalovirus (CMV) as a model, Phil Greenberg and Stan Riddell developed methods to identify and isolate CMV-reactive T cells from bone marrow donors, expand them *in vitro* using CD3/CD28 stimulation, and infuse these cells into patients post-transplant. Impressively, these adoptively transferred T cells reconstituted anti-CMV immunity, protecting patients from CMV disease. This was the first example of the successful transfer of antigen-specific cellular immunity from one human to another.[2]

Efforts then turned to developing methods to identify tumor-specific or tumor-associated antigens in humans, isolate T cells reactive with these antigens, expand them, and use them therapeutically. These efforts proved to be extraordinarily labor-intensive and only rarely successful. A solution finally emerged from the pioneering work of Zelig Eshhar and Michel Sadelain. Rather than search for tumor-reactive T cells in the patient, they created them

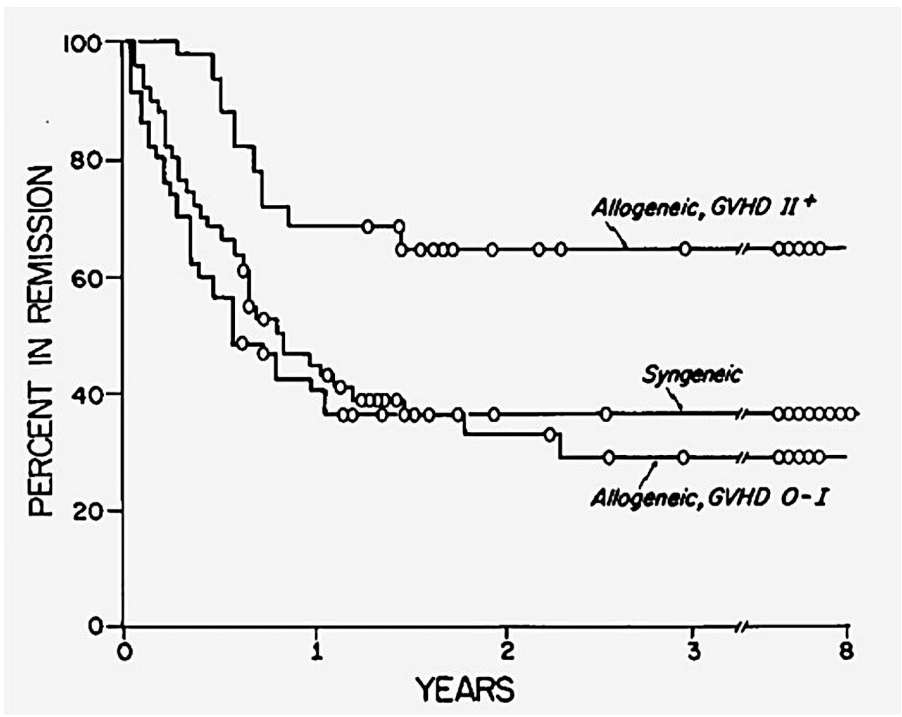

Figure 1. Kaplan-Meier estimate of the probability of remaining in remission of acute leukemia as a function of time after transplantation. Each open symbol represents one patient alive in remission. GVHD: graft-*versus*-host disease. Figure reproduced, with permission, from the paper by Weiden *et al*.[1]

by inserting tumor-reactive B-cell (and later T-cell) receptors. Today, Food and Drug Administration-approved adoptive T-cell therapies exist for patients with acute and chronic lymphocytic leukemia, B-cell lymphoma, multiple myeloma, melanoma, and synovial sarcoma. Admittedly, these therapies are imperfect and expensive, but the pace of progress is impressive, and I suspect we will soon have methods to genetically alter T cells *in vivo*. All of this starting from the observation of the GvL effect.[3]

Disclosures

No conflicts of interest to disclose.

References

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