Hematopoietic cell transplants for acute leukemias

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TITLE	One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation.
AUTHORS	Thomas ED, Buckner CD, Banaji M, *et al.*
JOURNAL	Blood. 1977;49(4):511-533. PMID: 14751.

Hematopoietic cell transplants are an important therapy of acute leukemias with more than one million worldwide. Sometimes a transplant is the preferred therapy or the *standard-of-care*. The initial concept underlying the use of transplants to cure acute leukemias was to give very intensive chemotherapy and/or ionizing radiation followed by rescue of hematopoiesis by infusing bone marrow cells from a HLA-matched donor. The intensive therapy would eradicate the leukemia and the graft would restore normal bone marrow function. In 1977 Thomas and colleagues published their landmark article in *Blood* describing outcomes of 100 consecutive subjects with advanced acute lymphoid or myeloid leukemia receiving transplants from HLA-identical siblings.[1] They reported median survival of about 4 months with 13 alive in remission 1-4½ years after transplantation (Figure 1). The authors noted subjects in a "*fair clinical condition*" did the best, concluding: "*[M]arrow transplantation should now be undertaken earlier in the management of people with acute leukemia who have an HLA-matched sibling marrow donor.*" As is said: "*The rest is history*" (Sufi poets, King Solomon or John Wade's British History, Chronologically Arranged).

Where are we almost one-half century later? Advances in HLA-testing, large registries of volunteers and use of HLA-haplotype-matched relatives mean almost everyone with acute leukemia has a potential donor. Intensity of pretransplant conditioning regimens has been reduced such that more people are potential transplant recipients. Blood has mostly replaced bone marrow as a graft, perhaps because of hematologists fear of going into the operating room. Posttransplant cyclophosphamide is now the preferred way to prevent graft-*versus*-host disease. And we now know that part of the anti-leukemia efficacy of allotransplants is immune-mediated and closely associated with graft-*versus*-host disease (this was mentioned by Thomas *et al*. in their article).

However, several important issues remain unsolved, the most important being which persons with acute leukemia to transplant and when. Increasingly accurate prognostic models for risk of failing conventional therapy and testing for measurable residual disease inform these decisions at the cohort level but not at the individual level. But we are still arguing, for example, who with acute myeloid leukemia should receive a transplant in first complete re-

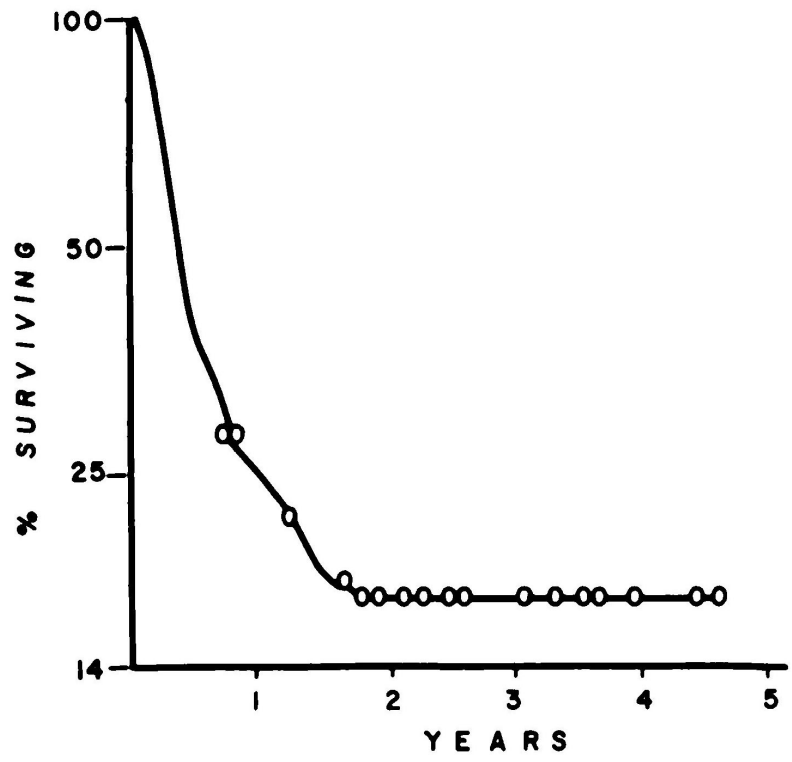

Figure 1. Kaplan-Meier plot of survival of the 100 patients with acute leukemia transplanted in the study by Thomas *et al*. Open circles represent surviving patients. Figure reproduced, with permission, from *Blood*.[1]

mission, whether post-remission therapy should be given pretransplant and whether someone who relapses should receive anti-leukemia therapy before advancing to a transplant. These issues are discussed in *Haematologica* and elsewhere.[2,3]

There are other issues to consider in the context of the report by Thomas and colleagues. First, this landmark article was rejected by several journals before making its way into *Blood*. Second, the article would have difficulty passing statistical review today. Third, Thomas and his team were considered radical for the main University of Washington campus and were exiled to a decaying US public service hospital before developing the Fred Hutchison Cancer Research Center. When Thomas and his team did the studies reported in their article most physicians had given up on transplants considering them too dangerous and unlikely to succeed in humans. Prominent hematologists claimed that Thomas *et al*. were exposing their patients to unacceptable risks.

An interesting question is whether a Human Subject Protection Committee would have allowed Thomas *et al*. to continue their studies. With a median survival of 4 months and only 13 survivors there must have been long intervals during which everyone died. At most hospitals today their work would have come to a screeching halt. And how many physicians would continue with this track record? Most people who think they have a great idea are wrong; Thomas was right. Fortunately for the many transplant recipients alive today Donn Thomas had an indomitable will to succeed and had the strong support of his wife Dottie. He was smart, was convinced the concepts were solid and had worked out the basics in rodents and dogs. He was convinced transplants would succeed and continued on against considerable resistance. Good timing helps: genetics of the HLA system had recently been revealed and he was surround by an all-star team who fervently supported him and his ideas. The Nobel Prize in Physiology or Medicine was a fitting tribute to Prof. E. Donnall Thomas. Are there lessons for us?

Disclosures

RPG is a consultant to Antengene Biotech LLC and Shenzen TargetRx; is Medical Director of FFF Enterprises Inc.; is a speaker for Janssen Pharma, BeiGene and Hengrui Pharma; sits on the Board of Directors of the Russian Foundation for Cancer Research Support; and is a member of the Scientific Advisory Board of StemRad Ltd.

References

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