Post-transplant cyclophosphamide: overcoming the HLA barrier to hematopoietic stem cell transplants

Andrea Bacigalupo
Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy.
E-mail: apbacigalupo@yahoo.com
https://doi.org/10.3324/haematol.2022.281256

TITLE	HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide.
AUTHORS	Luznik L, O'Donnell PV, Symons HJ, et al.
JOURNAL	Biology of Blood and Marrow Transplantation. 2008;14(6):641-650. PMID: 18489989

Matching for human leukocyte antigens (HLA) for transplants between donors and recipients has been a major area of research over the past half century: in the early seventies an HLA-matched sibling was required for optimal results. Recipients of transplants from HLA mismatched donors had dismal outcomes, with high mortality due to either rejection or acute graft-*versus*-host disease (GvHD).[1] The restriction of donors to HLA-matched subjects, initially siblings, prompted the institution of the International Unrelated Donor Registry, now comprising over 35 million individuals. In donors, and more so, in unrelated donors, allele matching for at least HLA A,B,C,DRB1, but possibly DQB1 and DP, has been shown to produce the best results and the lowest transplant-related mortality.[2] *Ex vivo* T-cell depletion was developed to reduce GvHD and allow the use of related HLA haploidentical donors: GvHD could be prevented, although graft rejection and immune reconstitution, with a high infectious-related mortality, remained problems for decades. A new sophisticated technology, capable of selective T-cell depletion ($\alpha\beta$), is now available and has improved the outcome of *ex vivo* T-cell-depleted haploidentical grafts.[3]

In a landmark paper published in 2008,[4] Luznik *et al.* reported an innovative way of removing alloreactive donor T cells in patients receiving a haploidentical graft, thereby allowing for successful engraftment with little or no GvHD. The method (I call it the revolution) is post-transplant high-dose cyclophosphamide (PTCY), 50 mg/kg on day +3 and day +4, followed by a calcineurin inhibitor and mycophenolate mofetil. The study came from Baltimore, where George Santos in 1966 had shown that high-dose PTCY could prevent GvHD from mismatched grafts in an animal model. However, despite these encouraging pre-clinical results, for over 30 years nobody really had the nerve to give 100 mg/kg of cyclophosphamide on days +3 and +4 post-transplant, because of the

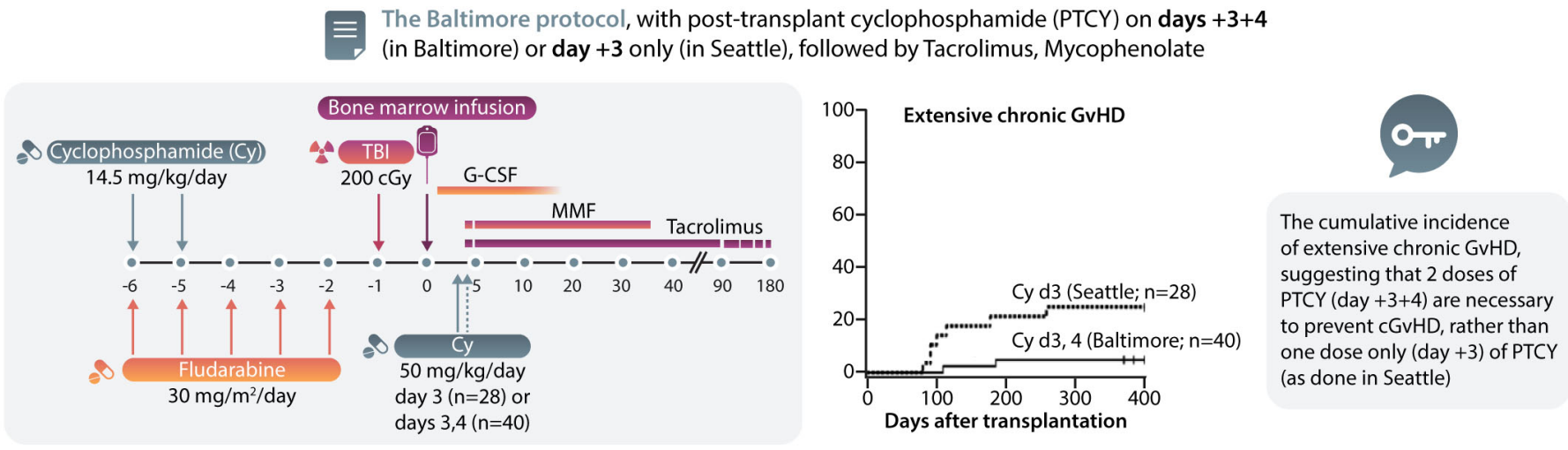

Figure 1. The original Baltimore protocol, designed for haploidentical related marrow grafts, as published in the *Biology of Blood and Marrow Transplantation* (2008). In this study post-transplant cyclophosphamide was given on days +3 and +4 in one group of patients (Baltimore) and on day +3 only in another group (Seattle), followed by tacrolimus and mycophenolate mofetil. The cumulative incidence of chronic graft-*versus*-host disease (GvHD) (shown on the right) suggested that two doses of cyclophosphamide are superior to one dose, in protecting patients from chronic GvHD. The conditioning regimen, although non-myeloablative, is highly immunosuppressive and allows the engraftment of mismatched grafts. Cy: cyclophosphamide; TBI: total body irradiation; G-CSF: granulocyte colony-stimulating factor; MMF: mycophenolate mofetil.

fear that the infused donor stem cells could be damaged.

However, when the Baltimore group published their clinical trial with haploidentical transplants in 2008,[4] it became immediately clear that high-dose PTCY was going to be a revolution in the field of allogeneic hematopoietic stem cell transplantation: in one move the authors had successfully crossed the HLA barrier, not with expensive sophisticated technology, but with a simple drug, accessible to everybody, given at a specific time, at a specific dose (that is the secret). PTCY kills alloreactive donor T cells, 72 hours after infusion, and leaves the remaining T-cell repertoire untouched: this is "selective *in vivo* T-cell depletion". This is why the use of PTCY has spread rapidly and successfully throughout the world.[5] PTCY is currently used not only in haploidentical grafts, but increasingly so in HLA-identical grafts, both from unrelated and related donors, in malignant and non-malignant disorders. PTCY has made haploidentical transplants as successful as HLA-related transplants (I could not believe my eyes when we started using PTCY in haploidentical grafts in 2009!). There is one last curious fact about this landmark paper: it was rejected by the New England Journal of Medicine, the Journal of Clinical Oncology and Blood, to appear (..only) in Biology of Blood and Marrow Transplantation, and to become the most cited allo-transplant paper in the past 20 years.

Disclosures

No conflicts of interest to disclose.

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