A potent and manipulable graft-*versus*-leukemia effect underpins the increasingly important role of transplantation in acute myeloid leukemia

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TITLE	Increased risk of relapse with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia.
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Increased donor availability and the advent of reduced intensity conditioning regimens now allow the routine delivery of allogeneic stem cell transplants in fit adults with high-risk acute myeloid leukemia (AML). Because of the potent anti-leukemic effect delivered by an allograft, consequent to both the conditioning regimen and the genesis of a graft-*versus*-leukemia (GVL) effect, European LeukemiaNet guidelines recommend that fit adults in first complete remission with a >40 % predicted risk of relapse should be considered as transplant candidates.[1] Transplant therefore represents the preferred consolidation therapy in younger adults with high-risk AML and in practice there are only a minority of fit adults over the age of 50 who are not now considered allo-mandatory.

Disease relapse remains the dominant cause of transplant failure and interventions with the ability to reduce the risk of disease occurrence are urgently required. Three distinct therapeutic opportunities present themselves. Firstly, novel induction regimens that can increase remission rates, particularly in patients with high-risk AML, have the potential to increase the number of transplant-eligible patients, at the same time as reducing induction, and potentially, transplant toxicity.[2] Venetoclax-based induction regimens show particular promise and the published results of randomized studies in fit allo-mandatory patients, such as the PARADIGM trial, are awaited with interest. Secondly, innovative conditioning regimens that deliver augmented anti-tumor activity without increased toxicity have the potential to reduce the relapse risk. To date, however, there is little corroborated evidence to support an alternative to fludarabine in combination with either busulphan or, in the setting of a reduced intensity allograft, melphalan as the conditioning regimen of choice. Finally, a range of post-transplant interventions designed to optimize the GVL effect are currently under investigation, building on the ability of post-transplant gilteritinib to improve outcomes in patients with minimal residual disease allografted for *FLT3*-ITD-positive AML.[3]

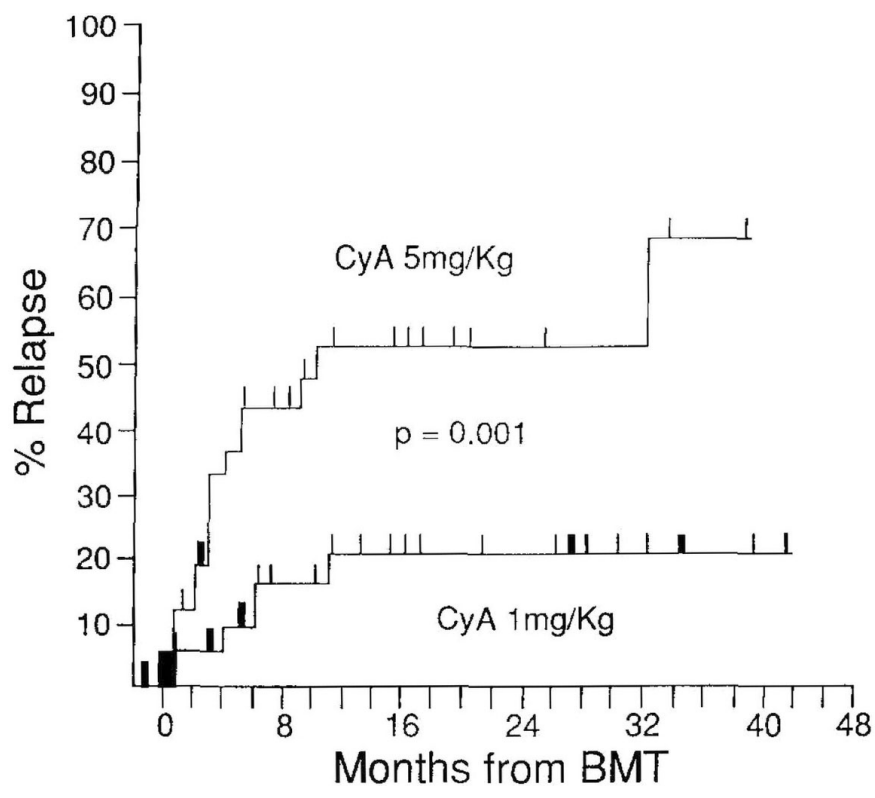

Figure 1. Impact of post-transplant immunosuppression intensity on relapse risk in patients allografted for acute myeloid leukemia. CyA: cyclosporine A; BMT: bone marrow transplantation. Figure reproduced, with permission, from Bacigalupo A, *et al.*[4]

Insights into the potency, and manipulability, of the GVL effect in patients allografted for AML are therefore critical in the design of innovative post-transplant strategies and the results of a randomized trial studying the impact of cyclosporine A (CsA) dose intensity on transplant outcome, conducted almost four decades ago, continues to inform transplant practice.[4] In this relatively small randomized trial 81 adults undergoing a myeloablative sibling allograft were randomized to receive either 1 or 5 mg/kg CsA/day for the first 21 days after transplant. Patients who received higher doses of CsA after their transplant experienced less acute graft-*versus*-host disease disease but a strikingly higher risk of disease relapse (40% *vs*. 13%, *P*=0.01) (Figure 1). Notably in multivariable analysis patients who received more intense post-transplant immunosuppression had a 9-fold increased risk of relapse.

What then are the lessons that we can learn from this pioneering randomized trial? Firstly, these data, which underscore both the potency and manipulability of the GVL effect in patients allografted for AML, highlight the importance of meticulously monitoring levels of post-transplant immunosuppression in routine clinical practice if transplant outcomes are to be optimized. Secondly, they support early evaluation of post-transplant levels of minimal residual disease in patients at high risk of relapse with the aim of guiding post-transplant interventions to augment a GVL effect, such as rapid tapering of immunosuppression, prophylactic donor lymphocyte infusions or the administration of maintenance drugs such as oral azacitidine (CC486) or the SIPR modulator, mocravimod. Finally, they confirm the vital importance of prospective randomized trials designed to improve transplant outcomes and the concomitant value of networks to accelerate transplant trials, such as the US BMT CTN and the UK IMPACT models, if we are to improve outcomes in newly diagnosed fit adults with AML.[5]

Disclosures

No conflicts of interest to disclose.

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