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Better acute graft-*versus*-host disease outcomes for allogeneic transplant recipients in the modern era: a tacrolimus effect?

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Acute graft-*versus*-host disease (GvHD) continues to be an important complication following allogeneic hematopoietic stem-cell transplantation (HSCT) in the modern era. With matched related and unrelated donors, the cumulative incidence of acute GvHD remains approximately 40-60%, respectively.[1] Survival outcomes for patients undergoing HSCT have however improved over the last few decades because of improvements in non-relapse mortality rather than relapse incidence.[2,3] It is an interesting conundrum that improvement in non-relapse mortality and survival has occurred despite a lack of sentinel advancements in acute GvHD prophylaxis or treatment. Calcineurin inhibitors are the cornerstone of prophylaxis, while steroids remain the mainstay of treatment.[4] The question arises whether improvements in non-relapse mortality and survival are due: (i) solely to improved management of acute GvHD complications (infections and organ toxicity); (ii) to better rates of acute GvHD response to steroid-based therapy; or (iii) to a secular shift in the nature and severity of acute GvHD over time.

Khoury *et al.* now offer some insights into these important questions in this issue of Haematologica.[5] In a large registry analysis (n=2905) from the Center for International Blood and Marrow Transplant Research (CIBMTR), they evaluate the incidence and outcomes of grade II-IV acute GvHD developing within 100 days after myeloablative, HLA-matched HSCT over three successive time periods [1999-2001 (n=497), 2002-2005 (n=962), 2006-2012 (n=1446)]. These periods overlap with important advances in supportive care (e.g., azoles for fungal infections, valacyclovir for cytomegalovirus).[6,7] The predominant GvHD prophylaxis regimens were tacrolimus-based (n=1767; 60.7%) or cyclosporine (CsA)-based (n=1077; 37.1%). Patients in the tacrolimus and CsA groups were well-balanced with regard to baseline characteristics (except for more matched unrelated donor and peripheral blood stem-cell grafts in the tacrolimus cohort). The authors then compared the outcomes of patients in each time period stratified by GvHD prophylaxis (CsA-based *versus* tacrolimus-based) and grade of acute GvHD (grade II *versus* grades III-IV).

Several interesting observations resulted. Firstly, the severity of acute GvHD appears to have decreased over time. The proportion of patients with grades III-IV severe acute GvHD in the most recent time period (2006-2012) has decreased by 20% compared to that in the earliest time period (1999-2001). This could be due to a true decrease in acute GvHD severity or a drift within acute GvHD categories, with more grade II patients being identified and reported to the CIBMTR. Simultaneously, there are fewer patients with concurrent three-organ (gut/skin/liver) involvement in recent years compared to previous years, while the proportion of patients with gut acute GvHD with or without skin involvement has increased significantly. Secondly, on multivariate analysis, in the subgroup of HSCT recipients with grades II-IV acute GvHD who received tacrolimus prophylaxis, overall survival (Figure 1, from the original article) and non-relapse mortality have improved in the modern era. The improvement appears to be due to fewer deaths from organ toxicity and infection. Interestingly, this improvement is not seen in HSCT recipi-

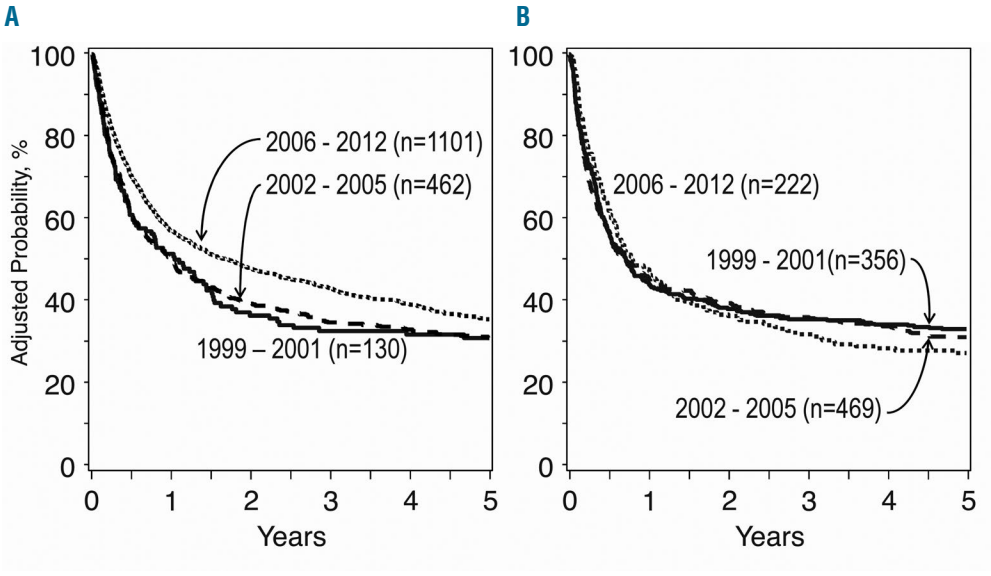

Figure 1. Overall survival. (A) Adjusted probability of overall survival following a diagnosis of grade II-IV acute GvHD among patients treated with tacrolimus-based GvHD prophylaxis. (B) Adjusted probability of overall survival following a diagnosis of grade II-IV acute GvHD among patients treated with cyclosporine-based GvHD prophylaxis. (Figure adapted from original article[5])

Table 1. Multivariate analysis results - effect of time cohort on overall survival and treatment-related mortality.

Grade II acute GvHD								
	Overall survival				Treatment-related mortality			
Tacrolimus	Year of transplant	Hazard ratio	Confidence interval	*P*-value	Year of transplant	Hazard ratio	Confidence interval	*P*-value
				0.0494				0.0397
	1999-2001	1.00			1999-2001	1.00		
	2002-2005	1.02	0.69-1.51	0.91	2002-2005	0.60	0.34-1.04	0.071
	2006-2012	0.80	0.55-1.16	0.25	2006-2012	0.51	0.30-0.87	0.013
Grade III-IV acute GvHD								
	Overall survival				Treatment-related mortality			
Tacrolimus	Year of transplant	Hazard ratio	Confidence interval	*P*-value	Year of transplant	Hazard ratio	Confidence interval	*P*-value
				0.19				0.0785
	1999-2001	1.00			1999-2001	1.00		
	2002-2005	0.98	0.71-1.37	0.92	2002-2005	0.90	0.62-1.30	0.56
	2006-2012	0.82	0.59-1.14	0.24	2006-2012	0.70	0.48-1.03	0.07

Adapted from original article[5]. GvHD: graft-*versus*-host disease.

ents with acute GvHD who received CsA prophylaxis. Finally, in the tacrolimus subgroup, it is the patients with grade II acute GvHD who have had a significant reduction in hazard for mortality and treatment-related mortality over time, rather than the patients with severe grades III-IV acute GvHD patients (Table 1, adapted from the original article[5]).

There could be a number of reasons for these findings. The authors speculate that the changes in acute GvHD severity and organ involvement could be caused by changing practices in GvHD prophylaxis over time, with increased use of tacrolimus rather than CsA. While one alternative factor underlying the reduction in severity of acute GvHD could be better high resolution HLA-matching techniques, particularly in matched unrelated donor HSCT,[8] this should be applicable uniformly to both tacrolimus- and CsA-based regimens. In support of their conjecture, results from randomized phase III trials in HLA-matched HSCT have shown that tacrolimus-based prophylaxis is associated with less acute GvHD (both grades II-IV as well as III-IV), albeit with similar overall survival, infections and relapse, when compared to CsA-based prophylaxis.[9] A number of other subsequent trials have echoed these results.[10–12] Consequently over the years, most transplant centers have adopted tacrolimus-based GvHD prophylaxis. This is reflected in the authors' data, with tacrolimus-based prophylaxis having largely replaced CsA-based prophylaxis, being used in 80% of cases in the 2006-2012 period compared to 27% in the 1999-2001 period.

The improvements in non-relapse mortality and overall survival in acute GvHD patients, on the other hand, almost certainly reflect improvements in supportive care and infection prophylaxis/treatment in transplant recipients. Thus, even when patients develop acute GvHD, they have an improved chance of survival. This was also suggested in a prior study by El-Jawahiri *et al.*,[13] in which

improved overall survival and treatment-related mortality were seen in patients with grade IV acute GvHD. This effect is not seen in CsA recipients in this study; however, this may simply reflect the limited numbers treated with CsA-based regimens in the modern era. We could also speculate that, in the current era, there is better management of tacrolimus toxicity and more stringent monitoring of tacrolimus drug levels, also perhaps accounting for better outcomes.

In summary, the current study traces secular trends in the incidence of acute GvHD, demonstrating that the severity of this complication has decreased over time, with a concomitant reduction in three-organ involvement (gut/skin/liver). It is a plausible but unproven inference that these improvements are related to increased utilization of tacrolimus-based prophylaxis (*versus* CsA-based). Furthermore, in the tacrolimus-treated subgroup, acute GvHD patients with milder manifestations (grade II disease) have had improved non-relapse mortality and survival, with reduction in deaths from organ toxicity and infection. Overall, these results reflect the strides made in transplantation practice, where improvements in infection management, supportive care, more stringent monitoring of immunosuppressive drugs, such as tacrolimus, as well as early recognition and management of drug toxicities, can lead to improved outcomes even in the absence of radical advances in acute GvHD therapy. Major therapeutic advances are however still awaited for those with severe acute GvHD (grades III-IV), who are in the most need.

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