Towards rational graft-*versus*-host disease prophylaxis

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Calcineurin inhibition for graft-*versus*-host disease (GvHD) prophylaxis was introduced into clinical practice of bone marrow transplantation about 35 years ago. Through the early work of Storb, Deeg and Ringden it became clear that calcineurin inhibition with cyclosporine A as a single agent was more effective than methotrexate alone and that the two drugs acted synergistically (see Table 1 for overview). Since then, multiple strategies have been tested in randomized trials: modified doses of cyclosporine A and another calcineurin inhibitor (tacrolimus), T-cell depletion (antithymocyte globulin, CD8 antibodies), cytokine blockade (CD1 antibodies, CD25

Table 1. Efficacy of drugs used alone and in combination for the prophylaxis of acute graft-*versus*-host disease.

Year	Author	N.	Arm A (acute GvHD incidence %)	Arm B (acute GvHD incidence %)	Journal	Follow-up study
1985	Deeg	56	MTX 75%	CYA 45%	Leuk. Res	
1985	Deeg	75	MTX 56%	CYA 33%	Blood	1989
1985	Storb	48	MTX 45%	CYA 42%	Blood	1989
1986	Ringden	59	MTX 22%	CYA 44%	BMT	
1986	Storb	46	MTX 53%	CYA-MTX 18%	Blood	1989
1990	Mrsic	76	CYA 51%	CYA-MTX 25%	BMT	
1990	Storb	122	CYA-MTX 35%	CYA-MTX-P 45%	Blood	
1991	Ringden	40	CYA-MTX 8%	CYA 47% MTX 26%	BMT	
1991	Ringden	48	CYA-MTX 12%	TCD 23%	BMT	1994
1991	Atkinson	41	CYA-MTX 15%	CYA-MTX-P 10%	AustNZJMed	
1993	Chao	150	CYA-P 23%	CYA-MTX-P 9%	NEJM	1999
1994	Nimer	38	CYA 80%	CYA-CD8depl 20%	Transplantation	
1995	Blaise	101	CYA-MTX 38%	CYA-MTX-aIL25 40%	Lancet	
1997	Deeg	122	CYA 76%	CYA-P 60%	Blood	
1998	Bacigalupa	60	ldCYA 61%	ldCYAldMTX 34%	Blood	
1998	Paolucci	59	CYA 1mg/kg n.r.	CYA 3mg/kg n.r.	BMT	
1998	Ratanathararhorn	332	TAC 32%	CYA 44%	Blood	
1999	Beelen	134	CYA-MTX 50%	CYA-MTX-Decont 25%	Blood	
2000	Locatelli	59	CYA 1mg/kg 57%	CYA 3mg/kg 38%	Blood	
2000	Chao	379	CYA-MTX 18%	CYA-MTX-P 20%	BBMT	
2000	Locatelli	71	CYA 37%	CYA-MTX 30%	Blood	
2000	Ratanathararhorn	180	CYA-MTX 74%	TAC-MTX 56%	Blood	
2000	Rutuu	108	CYA-MTX 56%	CYA-MTX-P 19%	Blood	
2001	Hiraoka	136	TAC 18%	CYA 48%	BMT	
2001	Winston	618	IVIG 100mg/kg 39%	IVIG 250mg/kg 42% IVIG 500mg/kg 35%	BMT	
2001	Bacigalupa	109	CYA 45%	CYA-Thymo 15mg/kg 11%; CYA-Thymo 7.5mg/kg 36%	Blood	
2002	Antin	13	CYA-MTX IL11	Nd; closed prematurely	BMT	
2002	Antin	186	CYA-MTX-aIL1 61%	CYA-MTX 59%	Blood	
2004	Bolwell	40	CYA-MTX 37%	CYA-MMF 48%	BMT	
2005	Wagner	405	CYA-TCD 18%	CYA-MTX 37%	Lancet	
2006	Blazar	100	CYA-MTX or TAC-MTX	+ Palifermin	Blood	2008
2007	Fong	95	CYA 14%	CYA-OH-Chloroquine 11%	BBMT	
2009	Finke	201	Local standard 33%	Local standard + ATG-F 11%	Lancet Oncology	2011
2010	Parmar	147	TAC-ldM 56%	+Pentostatin 0.5mg/kg 50%, 1 mg/kg 41%, 1.5 mg/kg 36%, 2 mg/kg 50%		
2012	Jagasia	155	CYA-MTX or TAC-MTX 17%	+Palifermin 16%	BMT	

CYA: cyclosporine A; MTX: methotrexate; P: prednisone; TAC: tacrolimus; IVIG: intravenous immunoglobulins; Thymo: rabbit antithymocyte globulin (thymoglobulin); Decont: gut decontamination; ATG-F: rabbit antithymocyte globulin, ATG-Fresenius; n.r.: not reported; Results selected from Pubmed search for "randomized controlled trial, gvhd, prophylaxis".

antibodies), biologics (interleukin-11, palifermin) and reducing inflammatory triggers (gastrointestinal decontamination) to mention only a few. The results of these trials cannot be compared directly because of differences in their designs. However, these trials have a common feature: they have failed to demonstrate a clear and clinically significant improvement in overall survival. The reasons for this were increased incidence of relapse, treatment-related mortality or both.

Severe GvHD is associated with high morbidity and mortality, consequently any significant reduction in the severity and incidence of GvHD should translate into measurable benefits in survival and quality of life. Obviously many of the studies done were not sufficiently powered to detect small changes in overall survival. An alternative explanation for studies showing decreased GvHD severity and incidence without survival benefit is expectation bias, as most studies were not appropriately blinded. There is no doubt that a drug combination diminishing the incidence of acute GvHD by more than half, as occurred in the study by Pidala *et al.*[1] published in this issue of the journal, would also be expected to result in at least a decrease in transplant-related mortality and should also produce detectable changes in quality of life outcomes.

The classical dilemma of hematopoietic stem cell transplantation, that GvHD can only be completely prevented at the expense of increased relapse, has been challenged by experimental work on regulatory T cells (T-reg). T-reg can be given by adoptive transfer of *ex vivo*-expanded cells or can be expanded *in vivo* if favorable conditions for the cells can be generated in the peri-transplant period. Because *in vitro* expansion of T-reg for adoptive transfer is extremely resource-intensive, *in vivo* expansion strategies are attractive. T-reg depend on interleukin-2 for their survival. Calcineurin inhibitors, by nature of their mechanism of action, diminish T-reg expansion and fuction in most settings. In addition, other pro-inflammatory cytokines that are abundant after conditioning prevent T-reg from expanding or skew them towards other T-helper lineages. In contrast to calcineurin inhibitors, sirolimus has been shown to allow for preferential T-reg expansion *in vitro* and *in vivo* in multiple studies.[2-4]

The rationale of the study presented by Pidala *et al.*[1] in this issue of Haematologica is to minimize the use of calcineurin inhibition while still preventing GvHD by preferential proliferation and proper functioning of T-reg. For this purpose the authors conducted a single center, randomized trial comparing their current standard of care, tacrolimus with plasma levels at 5-15 ng/L with methotrexate to sirolimus and tacrolimus at plasma levels of 3-7 ng/L. Tacrolimus was given at a lower dose in the experimental arm of the study in order to minimize the negative effects of calcineurin blockade on T-reg. The observed significant reduction of the incidence of acute GvHD (43% *versus* 89%) correlated with slightly increased Treg/total CD4 ratios on days 30 and 90 after transplantation. The incidence of chronic GvHD was 24% (95% CI 7-47%) for patients treated with sirolimus/tacrolimus and 64% (95% CI 41-79%) for those treated with methotrexate/tacrolimus, but survival and quality of life did not differ between the patients in the two treatment groups. In accordance with concepts based on experimental models, Pidala *et al.* present exploratory data showing a relative (but not absolute) expansion of T-reg that might be sufficient to explain the reduced incidence of GvHD. Whether this is really the mechanism that is instrumental in patients undergoing hematopoietic stem cell transplantation remains to be clarified. Other limitations of the study are the lack of relevant clinical outcome data other than GvHD (information on overall survival, transplant-related mortality and relapse incidence) as well as a remarkably high incidence of acute GvHD in the standard-treatment arm.

In summary, the results of this single center study are in concordance with the current concept of the biology of acute GvHD and the role of T-regs and also show how current treatment standards can be modified to serve new concepts. Whether this translates into meaningful changes in clinical practice will be answered when the results of the CTN 0402 trial comparing tacrolimus (5-10 ng/L)/methotrexate with sirolimus/tacrolimus (5-10 ng/L) are communicated in a few years time. The authors are to be commended for their continued effort to study this fascinating concept. In Europe in 2010 over 12,000 patients received an allogeneic HSCT. It is a pity that only a negligible fraction of them have been entered into randomized clinical trials.[5]

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