

EBV infection (CAEBV), EBV-associated hemophagocytic syndrome (EBV-AHS), peripheral T-cell lymphoma, chronic granular LPD, aggressive NK-cell leukemia, nasal/nasal type lymphoma, and hydroa vacciniforme.

Reduction and elimination of EBV-infected T/NK cells seems to be essential for the treatment of EBV-associated T/NK-cell LPD and it is important to distinguish it from ordinary EBV-associated B-cell LPD.^{8,9}

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To the editor:

Increased risk of leukemia relapse with high dose cyclosporine after allogeneic marrow transplantation for acute leukemia: 10 year follow-up of a randomized study

This is an update of a randomized study comparing low-dose intravenous Cyclosporin A (CyA) (1 mg/kg/day) with high dose CyA (5 mg/kg/day).¹ The results in 1991 suggested that disease-free survival was superior in patients receiving low-dose CyA, and this was mainly due to protection against leukemia relapse (Table 1). In that study 81 patients with acute leukemia (acute myeloid leukemia = 44; acute lymphocytic leukemia = 37; first complete remission [CR] = 53; >first CR = 28) were randomized to receive cyclosporin (CyA) 1 mg/kg intravenously (IV) or 5 mg/kg from day -1 to day +20. It is important to note that the average CyA serum levels were significantly different in the 2 arms only from day -1 to day +10 (295 ng/mL vs 686 ng/mL; *P* = .004), but not between day +11 and +20 (465 ng/mL vs 650 ng/mL, *P* = .1): this was due to the fact that patients in the CyA-1-mg arm had their dose increased beyond day +10 because of acute graft-versus-host disease (GvHD) and patients in the CyA-5-mg arm had their dose decreased due to toxicity.

Updated follow-up. The median follow-up for surviving patients is now 11.7 years with a minimum follow-up of 10 years (range 10.2-13 years). There have been 8 additional deaths, 4 in both arms: in the CyA-1-mg arm they were all caused by

transplantation-related complications (Table 1). This brings the crude transplantation-related mortality (TRM) in the CyA-1-mg arm from 27% to 38%. In the CyA-5-mg arm, the 4 additional deaths were caused by leukemia relapse in 2 patients and by transplantation complications in 2 patients. This brings the crude TRM in the CyA-5-mg arm from 25% to 30% and the relapse from 38% to 43%. Figure 1 outlines the actuarial 10-year TRM (Figure 1A), relapse (Figure 1B), and disease-free survival (Figure 1C) in the CyA-1-mg/kg vs CyA-5-mg/kg, respectively: TRM 39% vs 32% (*P* = .8), relapse risk 20% vs 59% (*P* = .002), and disease-free survival 49% vs 27% (*P* = .05). For patients in first CR the figures are as follows: TRM 28% vs 21% (*P* = .3), relapse risk 10% vs 45% (*P* = .01), and disease-free survival 56% vs 44% (*P* = .3). For patients with advanced disease (beyond first CR) the figures are TRM 46% vs 60% (*P* = .6), relapse risk 43% vs 100% (*P* = .03), and disease-free survival 36% vs 0% (*P* = .05).

The effect of patient age. TRM is significantly affected by patients age: 22% for patients aged 1 to 20 years, 21% for patients aged 21 to 30 years, and 71% for patients older than 31 (*P* = .02). There is no difference in TRM for patients receiving CyA 1 mg or CyA 5 mg in the 1 to 20 age group (27% vs 28%) or in the 21 to 30

Table 1. Comparative results in 1991 and in 2001

	Data analysis 1991		<i>P</i>	Data analysis 2001		<i>P</i>
	Cyclosporin dose			Cyclosporin dose		
	1 mg	5 mg		1 mg	5 mg	
No. of patients randomized	41	40		41	40	
Relapsed (%)	6 (15)	15 (38)	.01	6 (15)	17 (43)	.005
Alive (%)	24 (59)	15 (37)	.05	20 (49)	11 (27)	.04
Causes of death						
Relapse (%)	6 (15)	15 (37)	.01	6 (15)	17 (43)	.005
TRM (%)	1 (27)	10 (25)	.5	15 (37)	12 (30)	.3
Median FU (y)	2.7	1.7		13.1	12.1	
Range (y)	(0.9-3.8)	(0.7-3.6)		(11.4-14.2)	(11.0-14.0)	

FU indicates follow-up in years; TRM, transplantation-related mortality; GvHD, graft-versus-host disease.

age group (18% vs 24%) but this is not so in the group of patients older than 30 (89% vs 46%) ($P = .02$). As a consequence, the disease-free survival is superior for the CyA-1-mg/kg arm in patients younger than 30 years (60% vs 27%, $P = .05$) but not in patients older than 30 years (11% vs 27%, $P = .8$).

Conclusions. We confirm in this updated analysis, with a minimum follow-up of 10 years, that low-dose (1 mg/kg) CyA and low CyA serum levels in the first 10 days after an allogeneic BMT, confers significant protection against leukemia relapse both in patients with early or advanced leukemia. This has been confirmed in a randomized trial performed in children, comparing CyA 1 mg/kg vs CyA 3 mg/kg.² However, there is an increased risk of transplantation-related complications in the low-dose CyA arm, especially in patients older than 30 years. Therefore the increased antileukemic effect of GvHD is well tolerated by young patients but less so by older patients.

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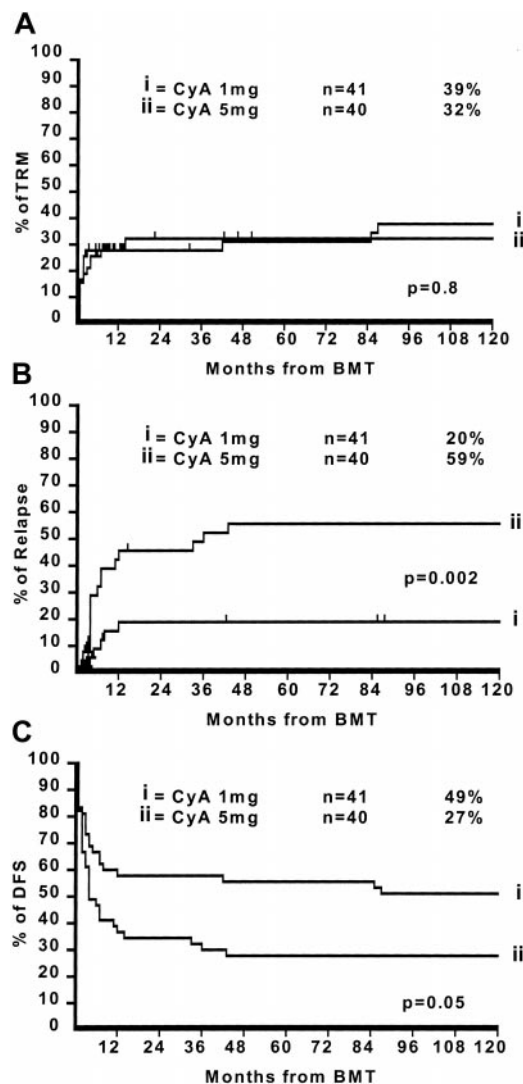


Figure 1. The 10-year TRM, relapse, and disease-free survival in the CyA-1-mg/kg vs CyA-5-mg/kg.