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LETTER TO THE EDITOR

The effect of administration order of BU and CY on toxicity in hematopoietic SCT in humans

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We read with interest the paper from Sadeghi *et al.*[1] recently published in your journal. The authors studied the effect of administration order of BU and CY as a conditioning regimen for hematopoietic SCT (HSCT) in a mouse model. They showed that inverting the order of BU–CY to CY–BU not only decreased conditioning-related toxicity significantly, but also allowed the same level of donor hematopoietic stem cell (HSC) engraftment. These data support earlier studies showing a potential benefit of CY–BU in animal models, and do encourage further investigation in humans.[2]

To test the possible effect on liver toxicity and clinical outcome of this approach, we started a clinical trial using CY–BU as a myeloablative conditioning regimen for HSCT in 2005.

The results were compared with those of a historical control of patients treated with a conventional conditioning regimen of BU–CY.

From September 2005 to November 2006, 11 patients were subjected to HSCT (nine allogeneic and two autologous) at the University Hospital (Federal University of São Paulo/UNIFESP), São Paulo, Brazil. Patients' characteristics are shown in Table 1. There was one case of aggressive non-Hodgkin's lymphoma, three cases of myelodysplastic syndrome, five cases of acute leukemia, one case of chronic myeloid leukemia and one case of severe aplastic anemia. The conditioning regimen consisted of CY 60 mg/m^2/kg on days −7 and −6 followed by oral BU 1 mg/kg administered every 6 h (total of 16 doses) on days −5 to −2. As post-grafting immunosuppression, all patients received a short course of MTX associated with CYA from day −1. The source of donor HSCs was peripheral G-CSF mobilized blood in seven patients and BM in four patients (one case of severe aplastic anemia, one case of CML and two cases of autologous patients). HSC were infused on day 0. All patients received as infection prophylaxis fluconazol, ciprofloxacin, acyclovir and sulfamethoxazol-trimetropin. Patients also received phenytoin for BU-related central nervous system toxicity. The historical control group consisted of 51 consecutive patients, treated in the same institution, from January 2001 to July 2005, using the same protocol of immunosuppression but with the conventional BU–CY conditioning regimen. Control patients' characteristics are shown in Table 1.

Liver toxicity

Liver toxicity was defined by the presence of hepatic sinusoidal obstruction syndrome (SOS) and elevation of serum transaminases (aspartate aminotransferase and alanine aminotransferase).[3] One patient (9%) treated with CY–BU and eight (15%) patients of the BU–CY group developed SOS before day +20 after HSCT. It is important to point out that one of the patients who developed SOS in the CY–BU group had chronic liver disease prior to HSCT. Alanine aminotransferase and aspartate aminotransferase serum levels were statistically higher in patients treated with BU–CY ($P = 0.03$) as shown in Figure 1. Bilirubin levels were also analyzed, showing a tendency to be higher in patients treated with BU–CY ($P = 0.07$).

Table 1 Characteristics of patients receiving CY–BU or BU–CY

	CY–BU	*BU–CY*
No. of patients	11	51
Age (range), years	40 (21–50)	32 (14–56)
Diagnosis		
MDS	3 (28%)	6 (12%)
RARS	1 (9%)	1 (2%)
RAEB	2 (19%)	4 (7%)
RAEB-t	0	1 (2%)
AML/ALL	5 (45%)	4 (8%)
1st CR	3 (27%)	2 (4%)
2nd CR	2 (18%)	2 (4%)
CML	1 (9%)	29 (57%)
Chronic phase	1 (9%)	23 (45%)
Accelerated phase	0	6 (12%)
Blast crisis	0	0
NHL	1 (9%)	3 (6%)
High-grade 2nd PR	1 (9%)	1 (2%)
Low-grade 2nd CR	0	2 (4%)
HL	0 (0%)	1 (2%)
MM	0 (0%)	1 (2%)
SAA	1 (9%)	7 (13%)
Donors		
HLA-matched sibling	9 (81%)	51 (100%)
Autologous	2 (19%)	0 (0%)
Source of HSC		
Peripheral blood	7 (63%)	35 (68%)
BM	4 (37%)	17 (32%)

Abbreviations: HL = Hodgkin's lymphoma; HSC = hematopoietic stem cell; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; RAEB = refractory anemia with excess blasts; RAEB-t = RAEB in transformation; RARS = refractory anemia with ringed sideroblasts; SAA = severe aplastic anemia

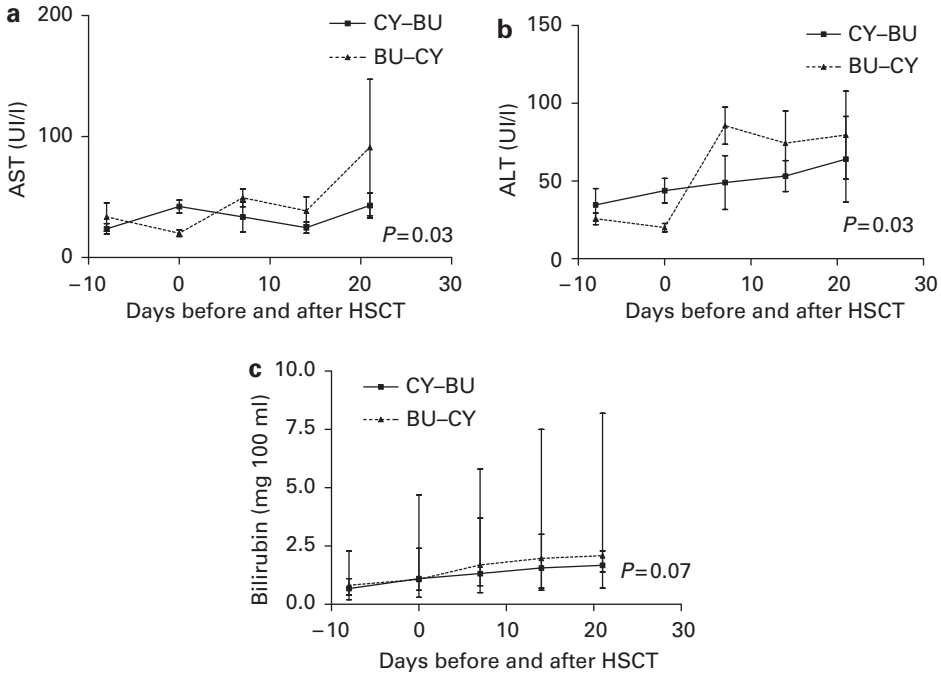

Figure 1 Serum AST (**a**), ALT (**b**) and bilirubin (**c**) of patients submitted to hematopoietic SCT (HSCT) after conditioning regimen with BU–CY ($n=51$) or CY–BU ($n=11$). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Engraftment

There was no engraftment failure in either group and the median time of neutrophil engraftment was 14 days in both the treated groups (range, 12–19 days for CY–BU and 11–22 days for BU–CY). Chimerism analysis was done by sex-mismatched FISH technique in four patients of the CY–BU group, showing 100% of donor chimerism on day +100 post HSCT. In the BU–CY group, chimerism analysis was done in 12 patients, showing 100% of donor chimerism by day 100 post transplantation.

GVHD and mortality

In the CY–BU group, five (45%) patients are alive and in CR of primary disease, in a media follow-up of 20 months (range, 18–22). There was no relapse-related mortality. Death causes of this group were related to GVHD and infection. Two patients died before day +100, secondary to GVHD and infection/SOS, respectively. The patient who developed fatal SOS was the one who had chronic liver disease before HSCT. In the BU–CY group, 26 (51%) patients were alive and in CR, and 100-day and 1-year TRMs were 18% and 16%, respectively. Four (44%) out of nine patients in the CY–BU group who received allogeneic HSCT developed grade II–IV acute GVHD,whereas two developed extensive chronic GVHD. In the BU–CY group, 20 (39%) patients developed grade II–IV acute GVHD and 24 (47%) extensive chronic GVHD.

The myeloablative conditioning regimen BU–CY has been widely used in patients subjected to both autologous and allogeneic HSCT. Despite the effectiveness of this conditioning regimen in hematologic diseases, liver toxicity such as SOS and acute hepatocyte damage occurs in up to 40% of HSCT recipients.[3] Although successful attempts at reducing hepatic toxicity have been developed, such as targeting BU plasma-concentration and using i.v. formulation, transplant-related toxicity remains a clinical problem to be overcome.[4–6]

In our cohort of patients treated with CY–BU, significantly less hepatic toxicity was observed and neutrophil engraftment did not differ from that in patients treated with BU–CY. These findings are in accordance with the data presented by Sadeghi *et al.*[1] in mice models supporting the use of CY–BU in larger prospective clinical trials.

Of note, neither our patients nor the mice studied by Sadeghi *et al.*[1] received target BU (^{T}BU). Therefore, we can speculate that using CY-^{T}BU may produce even less toxicity while keeping its myeloablative properties.

We are aware that our limited number of patients could have jeopardized statistical analysis in regard to incidence of GVHD, TRM and disease-free survival. Despite this fact we believe that our findings will encourage prospective trials using CY–BU not only to reduce liver toxicity but also to develop a more effective conditioning regimen.

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