Pediatric Hematology

Efficacy and safety of recombinant urate oxidase (rasburicase) for treatment and prophylaxis of hyperuricemia in children undergoing chemotherapy

Rasburicase has been defined as a potent urolytic agent for management of malignancy-associated hyperuricemia. We reviewed the data of 26 children with malignancy at risk for TLS who received rasburicase for treatment or prophylaxis of acute hyperuricemia, producing a significant decrease in uric acid level in all the patients. Tolerance of treatment was excellent. Rasburicase is a safe, highly and rapidly effective agent in the treatment and prevention of malignancies-associated acute hyperuricemia.

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TLS (tumour lysis syndrome) is a rare, but potential fatal, metabolic complication that can arise from treatment of rapidly proliferating and drug-sensitive neoplasms.[1] Prophylactic measures had considerably decreased the incidence of TLS and the morbidity associated with TLS. Rasburicase (R), a recombinant urate-oxidase has been defined as a well tolerated and potent urolitic agent for the treatment and prophylaxis of malignancies-associated acute hyperuricemia,[2,3] resulting significantly more effective than allopurinol in lowering uric acid levels (UAL) in patients at high risk of TLS.[4]

We retrospectively analyzed 26 consecutives children who received, for treatment or prophylaxis of hyperuricemia, R in 8 AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) Centres. Twelve pz (46.2%), 8 B-ALL, 3 solid tumor, 1 NHL, had hyperuricemia (group 1, treatment group) whereas 14 pz (54%), 7 NHL, 4 AML, 3 B-ALL had normal or moderately increased UAL (group 2, prophylaxis group). Normal values were defined according age (<5; 5-10; > 10 years) and gender at onset. At presentation the mean UAL±SD was 13.7±3.4 mg/dL and 4.0±1.7 mg/dL for patients in group 1 and group 2, respectively. Other metabolic abnormalities present at baseline were: serum creatinine ≥1.3 mg/dL in 5 patients (19%) and serum phosphate ≥ 7.0 mg/dL in 3 (11%). Baseline characteristics of the patients are shown in Table I. R was administered in 19 patients at the first induction chemotherapy 0-48 hours before the initiation of antiblastic infusion and in 7 during chemotherapy for relapse at 0.20 mg/kg i.v daily for median duration of 4 days (1-11). All patients showed a significant (p<0.001) reduction of UAL 48 h after treatment (group 1: 0.71 ±0.64 mg/dL, group 2: 1.18±1.14 mg/dL). R produced a highly significant (p<0.001) decrease in UAL within 24 hrs after the first injection (group 1: 0.51±0.39 mg/dL, group 2:1.83±1.07 mg/dL) with a response rate of 100% and 93% respectively. Two group 2 patients showed a transient increase in UAL during treatment. No patients needed a R supplementary daily dose for controlling UAL. Normalization of creatinine and phosphorous levels was obtained after 5 and 4 days respectively the beginning of treatment. Only a child with Wilms' tumor developed acute renal failure (ARF) without requiring dialysis. In all cases the treatment with urate-oxidase was associated with hyper-hydration (2-3 L/m^2 daily), and in 19 cases (73%) with urine alkalinization. Our experience confirms that R is a safe and high effective drug, capable

Table 1. Patients' Characteristics.

Total	26
Sex (M/F)	15/11
Age median, years (range)	7 (0-18)
Malignancies	
B-ALL	11 (42%)
NHL	8 (31%)
AML	4 (15.5%)
Solid tumor	3 (11.5%)

Groups	*Hyperuricemic*	*Non-hyperuricemic*
Cases	12 (46%)	14 (54%)
WBC (x10^9/L)	89.6 (0.7-712)	35.0 (3.6-162)
LDH (U/L)	5427 (402-15380)	616 (180-1159)
UAL (mg/dL)	13.73 (8-21.3)	3.98 (0.1-7.9)
Creatinine (mg/dL)	1.23 (0.3-2.5)	0.52 (0.2-0.8)
BUN (mg/L)	0.80 (0.2-1.4)	0.24 (0.1-0.43)
Phosphate (mg/dL)	5.6 (3.4-8.5)	4.6 (2.9-5.5)

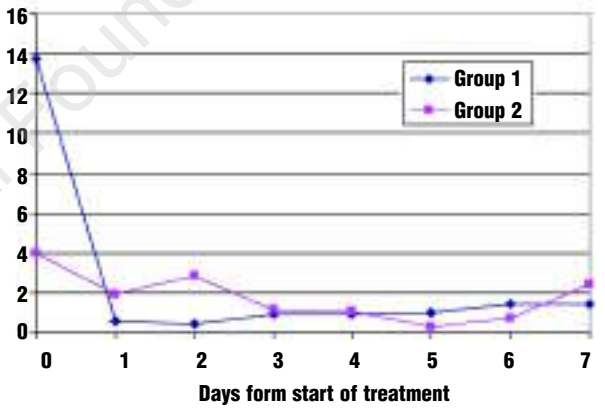

Figure 1. Comparison of plasma UAL during treatment with recombinant urate-oxidase and chemotherapy in Group 1 (treatment; n=12) or Group 2 (prophylaxis; n=14).

to induce a rapid and marked decrease in UAL within 24 hrs of the first injection. Rasburicase was well tolerated in all our patients, this being an important advantage over the non-recombinant enzyme, in particular considering the severe hypersensitivity reactions which sometimes occured with the latter.[5] This would suggest its use (at the dosage of 0.20 mg/kg for at least 5 days) in children defined at high risk of TLS by clinical (AML, ALL with leukemia/lymphoma syndrome, B-ALL FAB L3, stage III/IV NHL, bulky disease, renal impairment) or laboratory criteria (WBC ≥ 50×10^9/L, LDH ≥2 times over normal range, UAL ≥7 mg/dL, creatininemia or Ccr, cm×0.55/creatinemia, over normal range for age). Patients at low risk would be treated with standard therapy (allopurinol, hyper-hydration and urine alkalinization) and a single dose would be however taken into account for this last class of patients.[6] The steady improvement of renal function during treatment with R

in patients having impaired renal function at presentation, none of whom required dialysis, is remarkable. Probably, in same specific cases, a precise evaluation of renal function would be done by Schwartz formula (Ccr) or cystatin C. The low incidence of ARF associated with the absence of toxicity suggest anyway that this drug is cost-effective.

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