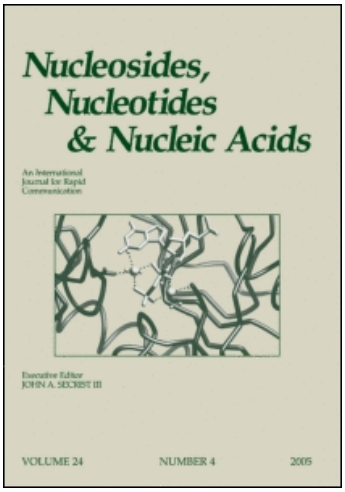

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Management of Hyperuricemia with Rasburicase Review

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ABSTRACT

Tumor lysis syndrome (TLS) is a serious complication in patients with hematological malignancies. Massive lysis of tumor cells can lead to hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcaemia. These metabolic disturbances may result in renal failure, because of precipitation of uric acid crystals and calcium phosphate salts in the kidney. The standard prophylaxis or treatment of hyperuricemia consists of decreasing uric acid production with allopurinol and facilitating its excretion by urinary alkalinization and hyperhydration. By inhibiting the enzyme xanthine oxidase, allopurinol blocks the conversion of hypoxanthine and xanthine into uric acid. An alternative treatment is urate oxidase which oxidates uric acid into allantoin. Allantoin is 5–10 times more soluble than uric acid and is therefore excreted easily. In several clinical trials rasburicase, the recombinant form of urate oxidase, has shown to be very effective in preventing and treating hyperuricemia. Rasburicase, in contrast with the non-recombinant form of urate oxidase uricozyme, is associated with a low incidence of hypersensitivity reactions. In addition to the demonstrated clinical benefit, rasburicase also proved to be a cost-effective option in the management of hyperuricemia.

Key Words: Rasburicase; Tumor lysis; Hematological malignancies.

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INTRODUCTION

Tumor lysis syndrome (TLS) is a potentially life-threatening complication associated with rapidly proliferating and drug-sensitive malignancies, such as leukemia and lymphoma. Massive lysis of tumor cells can lead to metabolic disturbances characteristic of TLS, including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcaemia. These abnormalities can result in cardiac and neurological complications, but can also lead to renal failure, particularly because of the deposition of uric acid crystals in the renal tubule and the distal collecting system of the kidney.[1–3] These crystals arise because uric acid, produced by the breakdown of nucleic acids in the liver, is poorly soluble in acidic urine (Fig. 1).

Other mechanisms contributing to renal failure in TLS are the precipitation of xanthine or calcium phosphate salts in the kidney.[1–3]

The incidence of hyperuricemia and TLS in patients with hematological malignancies is approximately 19% and 5%, respectively.[4,5] Patients with mature B-ALL or Burkitt's lymphoma have the highest incidence of TLS (>8%).[5] About 15–20% of the patients with TLS die as a result of TLS related complications.[4]

In most countries the standard prophylaxis or treatment of hyperuricemia and TLS consists of allopurinol, urinary alkalinization and hyperhydration.[1–3,6,7] Allopurinol, a xanthine analogue, inhibits xanthine oxidase, thereby reducing the production of uric acid (Fig. 1). Urinary alkalinization (by the administration of sodium bicarbonate) and hyperhydration increase the excretion of uric acid, because crystallization of uric acid is prevented when urinary pH is maintained above 7.0.

An alternative treatment for hyperuricemia is urate oxidase, an enzyme which is present in most mammals but absent in humans as a result of a nonsense mutation in the gene for urate oxidase.[3] Urate oxidase oxidates uric acid into allantoin, which is 5–10 times more soluble in urine en therefore easily excreted (Fig. 1). The recombinant form of urate oxidase, rasburicase, is produced by a genetically modified Saccaharomyces cerevisiae yeast in which the cDNA cloned from a strain of Aspergillus flavus is expressed.[1,8,9] In contrast with non-recombinant urate oxidase, uricozyme, rasburicase is associated with a low incidence of hypersensitivity reactions.[1,8–11]

Rasburicase has several beneficial features compared to allopurinol. First, rasburicase has a very rapid onset of action. Uric acid levels return to normal within a few hours. With allopurinol it may take several days, because patients still have

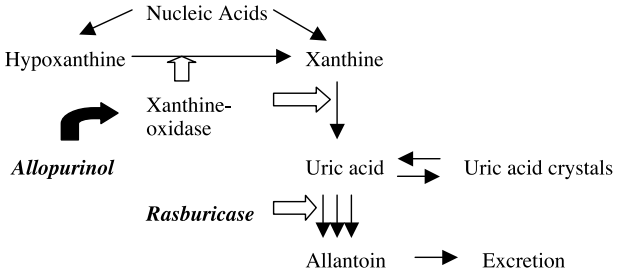

Figure 1. Breakdown of nucleic acids to uric acid.

to excrete the pre-existing uric acid.[3] Second, when using rasburicase xanthine nephropathy is prevented. Because xanthine oxidase is not inhibited, the very insoluble precursor xanthine does not accumulate. Another advantage is that urinary alkalinization is no longer needed when administering rasburicase. This reduces the risk of precipitation of xanthine and calcium phosphate salts which are better soluble in acidic urine.[3,12] The advantage of omitting urinary alkalinization for nursing practice is that it is no longer necessary to administer oral or i.v. sodium bicarbonate and to measure urine pH several times a day. Moreover, because the mean plasma terminal half life of rasburicase is approximately 17–20 hrs, it is sufficient to administer it once a day.[3,8,10] Finally, in contrast with allopurinol, rasburicase does not have interactions with drugs such as chlorpropamide, 6-mercaptopurine, azathioprine, dicumarol, cyclosporine and thiazide diuretics, as a consequence of which dosages of these drugs do not have be adjusted.[3]

A disadvantage of rasburicase is that it is contraindicated in patients with a G6PD deficiency, as it may induce hemolysis or methemoglobinemia.[3,7,10]

EFFICACY OF RASBURICASE

The efficacy of rasburicase has been evaluated in several clinical trials. A phase I study was conducted in healthy male volunteers, which were given rasburicase in escalating dosages (0,05 mg/kg to 0,20 mg/kg as a single dose or 0,10 mg/kg to 0,20 mg/kg as a 5-day course).[13] Rasburicase produced a rapid and marked decrease in uric acid levels within a few hours. The rate of decline increased with increasing dosage of rasburicase. The maximum tolerated dose of rasburicase was not reached and not further evaluated in this study.

Other studies involved pediatric and adult oncological patients with a high risk of hyperuricemia.

A phase II study included 131 children, adolescents and young adults with newly diagnosed leukemia or lymphoma who either presented with high uric acid levels or had large tumor burdens.[12] The study consisted of a dose validation phase to determine the most effective dosage and an accrual phase to evaluate efficacy and safety of rasburicase. The starting dosage in the dose validation phase was 0,15 mg/kg, based on the dosages used in the phase I trial. The dosage was then increased with 0,05 mg/kg to one that corrected hyperuricemia within approximately 48 hrs and

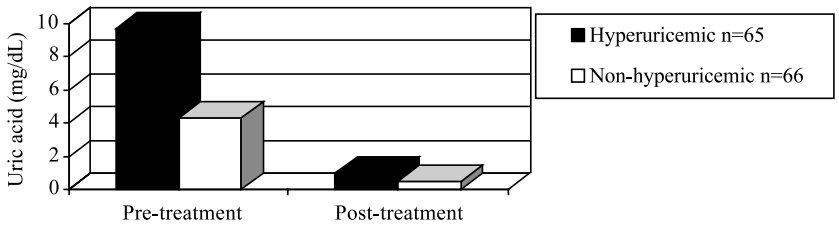

Figure 2. Decline in uric acid levels in hyperuricemic and non-hyperuricemic patients 4 hrs after the administration of rasburicase. Adapted from Ref. [12].

prevented hyperuricemia up to 24 hrs. Eventually a validated dosage of 0,2 mg/kg was used in the accrual phase. In both hyperuricemic and non-hyperuricemic patients rasburicase produced a rapid and dramatic decrease in uric acid levels of approximately 95–99%. In 65 patients who presented with hyperuricemia uric acid levels decreased from 9,7 to 1 mg/dL in 4 hrs after the first dose of rasburicase ($p = 0,0001$). In 66 non-hyperuricemic patients there was a decrease from 4,3 to 0,5 mg/dL ($p = 0,0001$) (Fig. 2). None of the patients developed renal failure after the start of rasburicase, in fact, there was a steady improvement of renal function during treatment. This is remarkable since in other studies, not using rasburicase, 20–25% of the patients with high risk of TLS required hemodialysis as a result of anuria, fluid overload or high creatinine levels.[5,14]

Two compassionate use trials have been performed. In the US, in the period of January 1999 to December 2000, 173 children and 72 adults with malignancy were treated with rasburicase (0,2 mg/kg) for 1–7 days.[15] In children presenting with hyperuricemia they found a decline in uric acid levels from 9,7 mg/dL at diagnosis to 0,6 mg/dL post-treatment ($p < 0,001$). In non-hyperuricemic patients there was a decline from 4,7 mg/dL to 0,5 mg/dL ($p < 0,001$). All but 2 patients achieved and maintained a normal uric acid level. In adult patients uric acid levels decreased from 11,9 mg/dL to 0,7 mg/dL ($p < 0,001$) in hyperuricemic patients and from 4,0 mg/dL to 0,7 mg/dL in non-hyperuricemic patients ($p < 0,001$) (Fig. 3). Because uric acid levels were only registered at diagnosis and 24–48 hrs after the last dose of rasburicase the rapidity of response could not be evaluated. Four children and six adults developed renal failure, eight of them presenting with renal insufficiency. Criteria for renal insufficiency were not displayed, but indications for hemodialysis were hyperphosphatemia ($n = 2$), uremia ($n = 5$) or both ($n = 3$). At the time hemodialysis was started all patients had low uric acid levels as a result of the administered rasburicase. The incidence of renal failure in this study is remarkably high, compared to other studies in which rasburicase was used.[12,16] This is possibly explained by the inclusion of highly selected patients with a particularly high risk of TLS and renal failure.

Another compassionate use trial performed in 9 countries in Europe included 166 pediatric patients and 112 adult patients with predominantly leukemia and lymphoma.[17] Hyperuricemic patients received a median of 6 doses of rasburicase (0,2 mg/kg) and non-hyperuricemic patients a median of 5 doses. Again there was a dramatic decrease in uric acid levels, with a 96,6% response rate in hyperuricemic patients and 100% in non-hyperuricemic patients. Mean uric acid levels in 29 hyperuricemic children decreased from 15,1 mg/dL to 0,8 mg/dL ($p < 0,001$) after

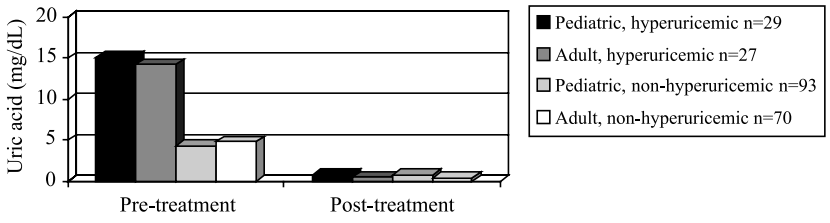

Figure 3. Decline in uric acid levels after several days of treatment with rasburicase. Adapted from Ref. [15].

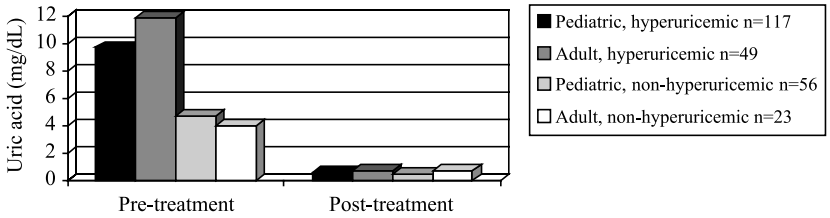

Figure 4. Decline in uric acid levels after several days of treatment with rasburicase. Adapted from Ref. [17].

treatment and from 4,4 mg/dL to 0,8 mg/dL ($p < 0{,}001$) in 93 patients who received prophylactic rasburicase (Fig. 4). In 27 hyperuricemic adults mean uric acid levels decreased from 14,2 mg/dL to 0,5 mg/dL ($p < 0{,}001$) and in the 70 non-hyperuricemic patients from 4,8 mg/dL to 0,4 mg/dL ($p < 0{,}001$). Three children and one adult patient required hemodialysis to manage acute renal failure. Again, uric acid levels were low as a result of the administration of rasburicase. Two of these patients died, non of which being related to rasburicase.

Only one randomized clinical trial comparing allopurinol to rasburicase has been performed.[16] In this study 27 pediatric patients received rasburicase during induction chemotherapy and 25 patients received allopurinol. Four hours after the first dose of rasburicase patients showed a 86% decrease in uric acid levels, whereas in patients treated with allopurinol there was only a 12% decrease ($p < 0{,}0001$) (Fig. 5). Moreover, patients treated with rasburicase had a more rapid decline and maintained lower mean uric acid levels during induction chemotherapy in comparison to patients treated with allopurinol. To quantify the exposure to uric acid during the first 96 hrs of treatment with chemotherapy, the area under the curve for mean uric acid was calculated (AUC_{0-96}). Using this $AUC_{0-96,}$ patients receiving rasburicase had a 2,6 fold less exposure to uric acid during the first 96 hrs of therapy (Fig. 5).

Because of the small sample size in this study, no conclusions concerning renal outcome could be drawn. Only one patient, treated with allopurinol developed renal failure. However, when evaluating creatinine levels over the first 96 hrs of therapy, hyperuricemic patients treated with rasburicase showed a steady decline in creatinine

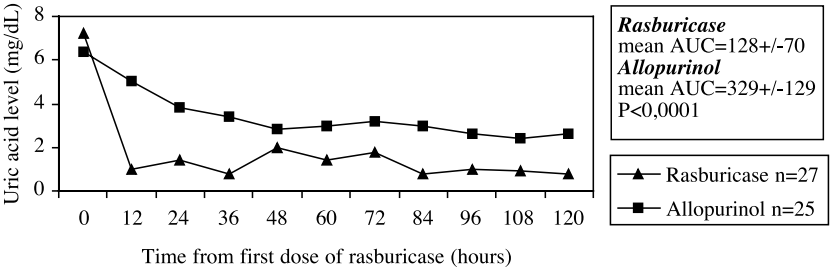

Figure 5. Uric acid levels over time after administration of rasburicase or allopurinol. Adapted from Ref. [16].

levels, whereas the creatinine levels of hyperuricemic patients in the allopurinol group worsened over the first four days of therapy.

SAFETY AND SIDE-EFFECTS

Rasburicase was generally well tolerated in the studies performed, with few, generally mild adverse events.

The 28 healthy volunteers receiving rasburicase in the phase I study did not experience any major adverse events, only two patients experienced headaches.[13]

In the phase II study performed by Pui[12] one patient had mild nausea and vomiting. Another patient developed bronchospasm and hypoxia. It was not clear whether this was related to the administration of rasburicase because the girl had presented with eosinophilia and pneumonia. Therefore the symptoms could also be related to the release of cytokines from eosinophils caused by chemotherapy. They also reviewed the development of antibodies against rasburicase. In 14% of the patients antibodies were detected, but no relationship with clinical symptoms or adverse events was found.

In the compassionate use trial in the US[15] 4 children and 5 adults had adverse events that were considered to be drug related or of unknown etiology. These adverse events included pruritus, hives, rash, wheezing, edema, vomiting, myalgia and headache. The development of antibodies was not evaluated in this study, but subsequent administration of rasburicase to 12 patients was not related to a higher incidence of adverse events.

In the compassionate trial in Europe[17] mild adverse events were registered. One drug related serious adverse event was observed in one adult patient with AML. He developed a grade 2 allergic reaction with grade 1 fever. Recovery was without sequela when rasburicase was discontinued and paracetamol administered.

Adverse events registered in the trial comparing rasburicase to allopurinol included fever, pain and mucositis, which were most likely secondary to the disease and chemotherapy.[16] No anaphylactic reactions to rasburicase were seen. In one patient rasburicase therapy was discontinued because of hemolysis, but no underlying G6PD deficiency was found. In 23 patients who had been given rasburicase, antibodies were determined in serum samples. None of these samples contained antibodies to rasburicase.

COST-EFFECTIVENESS

Regarding the very promising results of rasburicase in clinical trials, questions were raised about the cost-effectiveness of rasburicase, as rasburicase is far more expensive than treatment with allopurinol, hyperhydration and urinary alkalinization. Four days of treatment with rasburicase has an average of cost of EUR 2220 in adults and EUR 960 in children.[18] Recently a pan-European multicentre economic evaluation of rasburicase was performed to assess the incremental cost and cost-effectiveness of the introduction of rasburicase for prevention and treatment of hyperuricemia and TLS in comparison with current management.[18] Data from a

retrospective review in Europe concerning incidence and costs related to hyperuricemia and TLS were used.[4]

Cost-effectiveness of prevention and treatment of hyperuricemia and TLS with rasburicase was calculated by dividing the incremental cost of rasburicase by the average number of life-years saved, resulting in an incremental cost-effectiveness ratio (ICER) (Fig. 6). Using this formula it was assumed that the prevention or treatment of hyperuricemia and TLS with rasburicase resulted in a 90% reduction of hyperuricemia related costs and that TLS would be prevented completely by the administration of rasburicase (100% reduction of costs).

ICER of *prevention* ranged form EUR 23.794 to EUR 101.734 per life-year saved (LYS) in adults and from EUR 425 to EUR 3054 per LYS in children, the ICER in adult AML patients being relatively high because of limited life-expectancy (Table 1). ICER of *treatment* with rasburicase in adults ranged from EUR −24.033 to EUR 5.062 (Table 1). ICER of treatment in children were not shown, because treatment was already cost saving, which means that the costs of treatment with rasburicase were lower than costs associated with hyperuricemia.

Amounts of EUR 20.000 to EUR 30.000 per life-year or QALY were considered to be cost-effective in studies evaluating the cost-effectiveness of the use of statines in coronary heart disease and intensive treatment in type I diabetes patients.[18] Regarding these amounts, prevention with rasburicase in adults is cost-effective in ALL and NHL patients, whereas in children prevention is highly cost-effective in all indications. Treatment of hyperuricemia and TLS with rasburicase in adults is cost-effective and cost saving in children.

Because results in this study were based on assumptions, a number of sensitivity analyses in adult NHL and pediatric ALL patients were performed to test how solid the results were. Incidences of hyperuricemia and TLS and life expectancy were varied, which did not change overall conclusions. Because it was reasonable that rasburicase could not prevent all TLS-related problems, they also varied the anticipated efficacy profile. The assumption of 90–100% reduction of costs was changed into 60% and 80%. Assuming a 60% reduction, prevention as well as treatment with rasburicase

Incremental cost of prevention of hyperuricemia with rasburicase

(cost rasburicase)-(cost hyperuricemia x probability hyperuricemia x % hyperuricemia prevented) –
(cost TLS x probability TLS x % TLS prevented)

Incremental cost of treatment of hyperuricemia with rasburicase

(cost rasburicase)-(cost hyperuricemia x % hyperuricemia prevented) –
(cost TLS x probability TLS in case of hyperuricemia x % TLS prevented)

Costs per life-year saved

$$\frac{\text{Incremental costs of rasburicase}}{((\text{probability of TLS related mortality}) \times (\%\ \text{TLS prevented}) \times (\text{life expectancy}))}$$

Figure 6. Formula for calculating incremental costs and incremental cost-effectiveness ratio Adapted from Ref. [18].

Table 1. ICER of prevention and treatment in adults and children.

	Adults						Children		
	Prev.			Treatm.			Prev.		
Country	ALL	AML	NHL	ALL	AML	NHL	ALL	AML	NHL
Belgium	32.126	101.734	41.383	1.599	5.062	2.059	1.790	3.054	1.710
Netherlands	31.014	98.210	39.950	302	956	389	1.610	2.748	1.538
Spain	31.496	99.738	40.571	930	2.944	1.197	1.688	2.880	1.613
UK	23.794	75.348	30.650	−7.589	−24.033	−9.776	445	760	425
All countries	29.245	92.609	37.671	−1.344	−4.255	−1.731	1.325	2.260	1.265

(Adapted from Ref. [18].)

would remain cost-effective in children (range EUR −1.626 to EUR 3.388), whereas in adults only treatment would remain cost-effective (range EUR −4.443 to 7.833).

CONCLUSION

Reviewing clinical trials, rasburicase can be of great clinical benefit in oncological patients with a high risk of hyperuricemia or TLS. It is highly effective and appears to be superior to allopurinol, urinary alkalinization and hyperhydration. Moreover, rasburicase has a favorable safety profile and seems to be a cost-effective option in the management of hyperuricemia and TLS in oncological patients.

Regarding the promising results of rasburicase in oncological patients, in future it may also have a role in the treatment of patients with gout, especially in those who are resistant to standard therapy.

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