RASBURICASE AND HYPERURICEMIA IN CANCER PATIENTS

Generic (Trade Name): Rasburicase (Elitek™)

Manufacturer: Sanofi-Synthelabo Canada Inc.

Indication: For the treatment and prophylaxis of hyperuricemia in pediatric and adult cancer patients.¹

Current Regulatory Status: Rasburicase was approved by the US Food and Drug Administration (FDA) on July 16, 2002 for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma and solid tumour malignancies who are receiving chemotherapy that is expected to result in tumour lysis syndrome. Previous to this, it had been launched in Europe under the brand name Fasturetic.² A submission has been made to the Canadian Therapeutic Products Directorate in reference to rasburicase, and final approval is pending (David Pao, Sanofi-Synthelabo, Markham, ON: personal communication, 2003 Feb 3). Currently in Canada, it is available via the Special Access Programme.³

Description: Tumour lysis syndrome is a metabolic disturbance that can lead to increased morbidity and mortality. It is characterized by various combinations of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, resulting from cell destruction during cancer treatment. This frequently leads to acute renal failure. Tumour lysis syndrome usually occurs during or shortly after (1 to 5 days) chemotherapy. It is associated with the treatment of hematologic malignancies including Burkitt's lymphoma, acute lymphoblastic leukemia, and rarely with solid tumours.

Rasburicase, a recombinant urate-oxidase enzyme, converts uric acid into allantoin, a more soluble by-product of the purine catabolic pathway. The enzyme is administered intravenously (IV) at a dose of 0.2 mg/kg/day for up to seven days. In a pharmacokinetic trial using the approved dose for five days, the observed $C_{\text{max}}$ was 4.5 mg/L, and the mean elimination half-life was 21.1 hours.¹³⁴

Current Treatment: Prophylaxis in patients at high risk for tumour lysis syndrome consists of maintaining hydration, alkalization with sodium bicarbonate, administering allopurinol to reduce uric acid and monitoring serum chemistry. Acute situations may require hemodialysis and disruptions in chemotherapy.⁴

Cost: According to the publication The Medical Letter, the cost of five days of therapy is US$16,762 for a 30-kg child at the lowest usual daily dose (i.e. 0.15 mg/kg). The November 2002 Drug Topics Red Book Update was apparently used to obtain this figure.⁵
Evidence: **Rasburicase vs. Standard Treatment:** Evidence of comparative efficacy and safety is available from a single randomized trial. Patients (n=52) aged 0.3 to 17 years with leukemia or lymphoma were randomized to receive either rasburicase or allopurinol without blinding. All were scheduled to receive five to seven days of therapy at a dose of 0.2 mg/kg IV daily or 10 mg/kg po (300 mg/m²) divided every eight hours of rasburicase or allopurinol, respectively after initiation of anti-tumour therapy. In the case of allopurinol, investigators were allowed to change the allopurinol dose based on their own practice. Standard hydration and bicarbonate, if required, were allowed.

The protocol defined efficacy endpoints that included occurrence of renal complications, occurrence of hypertension, occurrence of metabolic abnormalities, incidence of elevated creatinine and the area under the curve (AUC) of the plasma uric acid concentration in the first 96 hours of therapy (AUC₀⁻⁹₆). The AUC₀⁻⁹₆ was the primary efficacy endpoint.

The incidence of renal complications was similar in both arms (one participant in the allopurinol arm required hemodialysis); the trial was underpowered to detect a statistical difference for this outcome. The incidence of hypertension was not reported. For both groups, the mean time from study drug administration to the first dose of induction chemotherapy was 21 hours. Using intent-to-treat analysis, the mean AUC₀⁻⁹₆ was 128 mg/dL/hr (95% CI: 114 to 142) and 329 mg/dL/hr (95% CI: 200 to 458) for rasburicase and allopurinol recipients, respectively (p<0.0001); this translated to 2.6 times less exposure to uric acid during the first 96 hours of therapy.⁶

**Rasburicase Alone:** Pui and colleagues have published the results of non-comparative trials in children, adolescents and adults, indicating that rasburicase is effective for the prophylaxis and treatment of hyperuricemia associated with underlying malignancy.⁷,⁸ Recently, the updated results from their compassionate-use trial were presented at the American Society of Clinical Oncology ASCO. The study population which consisted of 778 patients, both children and adults, showed that all patients "responded" to therapy administered prophylactically (100%) and most when used as a treatment (98-99%).⁹ Other trials examining the merits of rasburicase are available in abstract form.⁴,10-13

Adverse Effects: According to the product monograph, drawing from the experience of 703 patients, the commonly reported serious adverse reactions were serious fever (5%), neutropenia with fever (4%), respiratory distress (3%), sepsis (3%), neutropenia (2%), and mucositis (2%). A FDA "Black Box" warning appears on the US product monograph warning of infrequent (≤1%) but serious adverse events including anaphylaxis, serious rash, hemolysis, and methemoglobinemia. Rasburicase is contraindicated in those patients with glucose-6-phosphate dehydrogenase deficiency.¹⁴
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Commentary:
So far, there is no evidence that rasburicase reduces serious complications or death from tumour lysis syndrome compared to standard therapy. Unless more data from clinical trials become available, the effectiveness of this drug will require speculation based on surrogate endpoints from a single randomized trial of efficacy.

In addition, no comparative data are available for the adult population. A trial "assessing the respective places of allopurinol and rasburicase in ... adult patients" is part of the manufacturers commitment after licensing according to a European Commision Report.

Accordingly, a Canadian pharmacoeconomic analysis is in development (David Pao: personal communication, 2003 Feb 3) and will need to overcome these considerable hurdles in order to reliably aid formulary decisions.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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