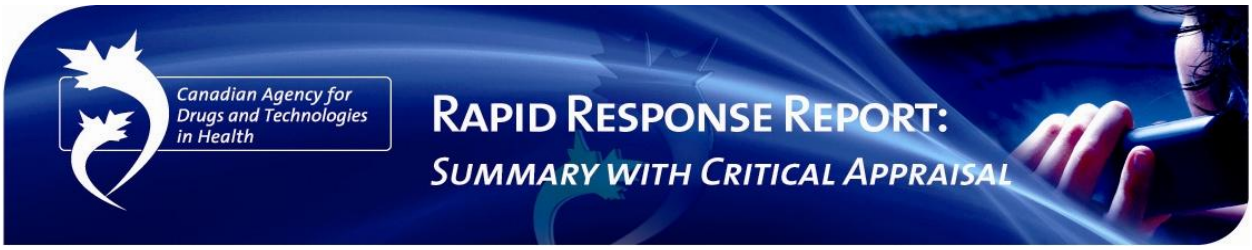


TITLE: Rasburicase for Adults with Acute Tumor Lysis Syndrome: A Review of Clinical and Cost Effectiveness and Safety

DATE: 20 March 2013

CONTEXT AND POLICY ISSUES

Tumor lysis syndrome (TLS) is a serious complication in patients with hematological malignancies that is characterized by rapid and severe metabolic abnormalities resulting from the massive lysis of tumour cells.[1-3] TLS is observed most commonly after the initiation of anti-cancer therapies in malignancies with high proliferative rates, large tumour burden, and high sensitivity to treatment.[1,3] The lysis of tumour cells will release large amounts of potassium, phosphate, nucleic acids and proteins into systemic circulation, resulting in hyperkalemia, hyperphosphatemia, hyperuricemia and uremia.[2-5] Clinical manifestations of TLS typically occur 12 to 72 hours after treatment initiation and may include renal failure, seizures, cardiac arrhythmias, and death.[1]

Uric acid, the end product of nucleic acid purine catabolism, is one of the main metabolites responsible for TLS complications.[4] Tumour cells contain a high nucleic acid content and an active purine metabolism.[2] Purine nucleic acids are reduced to hypoxanthine and xanthine and then degraded to uric acid by the enzyme xanthine oxidase.[2,3] Uric acid is poorly soluble in water and its overproduction and overexcretion can induce crystal precipitation and deposition in the renal tubules, potentially leading to acute renal failure.[2,3]

Nearly 35% of all patients that develop clinical TLS die, highlighting the importance of prevention and treatment.[2] Aggressive intravenous (IV) hydration is recommended prior to therapy in patients at risk for developing TLS in order to promote urinary excretion of uric acid and minimize the likelihood of precipitation in the renal tubules.[1,6] In addition to hydration, drugs have been developed for the treatment of hyperuricemia in TLS. Allopurinol is a structural analog of hypoxanthine that competitively inhibits xanthine oxidase to block the metabolism of xanthine and hypoxanthine to uric acid.[2,6] The inhibition of xanthine oxidase increases the concentrations of xanthine and hypoxanthine, which are subsequently converted to products that inhibit the purine biosynthesis pathway.[2] Although allopurinol blocks uric acid formation, it has no effect on pre-existing uric acid.

Rasburicase is a recombinant form of urate oxidase, which is an enzyme that catalyzes the oxidation of uric acid to the more water-soluble product allantoin.[2,6] Rasburicase is administered via a 30-minute intravenous infusion at a recommended dose of 0.2 mg/kg/day for 3 to 5 days and has been found to be effective for the management of plasma uric acid levels in both pediatric and adult patients.[2,4,5] In Canada, rasburicase (Fasturtec) is indicated for the treatment and prophylaxis of hyperuricemia in pediatric and adult cancer patients.[7]

The purpose of this review is to examine the clinical evidence regarding the use of rasburicase for adults to prevent or treat acute TLS in order to reduce the need for hemodialysis. In addition the cost effectiveness of rasburicase compared to allopurinol or hydration for adults with acute TLS will be examined.

RESEARCH QUESTIONS

1. What is the evidence for the clinical effectiveness of rasburicase for adults with acute tumor lysis syndrome to reduce or eliminate the need for hemodialysis?

2. What is the evidence for the safety of rasburicase for adults with acute tumor lysis syndrome?

3. What is the evidence for the cost-effectiveness of rasburicase compared with allopurinol or hydration for adults with acute tumor lysis syndrome to reduce or eliminate the need for hemodialysis?

KEY FINDINGS

Rasburicase was found to lower uric acid levels in adult cancer patients who had, or were at risk for developing, hyperuricemia or tumour lysis syndrome (TLS). Rasburicase was found to be well tolerated in adult cancer patients, with a low rate of adverse events, renal failure, or need for hemodialysis. No evidence on the cost effectiveness of rasburicase compared with allopurinol or hydration for adults with acute TLS was identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including MEDLINE, Embase, PubMed, The Cochrane Library (2013, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and February 19, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with, or at risk for, tumor lysis syndrome (TLS)
Intervention	Rasburicase (recombinant urate oxidase)
Comparator	Q1+Q2: Allopurinol, Hydration, Placebo, No Treatment Q3: Allopurinol, Hydration
Outcomes	Reduction or elimination of need for hemodialysis, Safety, Cost Effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were included in a selected systematic review, were case series or case studies, or were published prior to 2003.

Critical Appraisal of Individual Studies

The quality of RCTs and non-randomized studies were evaluated using the Downs and Black instrument.[8] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described. No economic evaluations were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 154 citations. Upon screening titles and abstracts, 139 citations were excluded and 15 potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were identified through grey literature searching. Of the 15 potentially relevant reports, eight did not meet the inclusion criteria. Seven reports were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One RCT, four prospective studies, and two retrospective studies met inclusion criteria. No economic evaluations were identified. Studies of potential interest that did not meet the selection criteria can be found in Appendix 2.

Summary of Study Characteristics

Details on study characteristics can be found in Appendix 3.

Study design and country of origin

One open-label RCT,[9] four prospective multicenter studies,[10-13] and two retrospective single-center studies[14,15] were included in this review. Of the prospective studies, two were compassionate use studies, one conducted internationally (Europe, Asia, Australia)[11] and one conducted in North America (Canada and USA).[13] The RCT[9] and one retrospective study[14] were

from the USA. One prospective study each was from Taiwan[10] and France.[12] One retrospective study was from Germany.[15]

Patient population

All studies included adult patients with hematological malignancies who were at risk for developing hyperuricemia or TLS as determined by high tumour burden, large tumour sizes, elevated lactate dehydrogenase levels, or elevated uric acid levels. The overall age of included patients ranged from a median of 54 to 67 years. In the RCT[9] and two prospective studies,[10,12] patients were undergoing chemotherapy, while therapy administered for the cancer was not specified in the other studies. All studies enrolled patients with various types of leukemia and lymphoma such as acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma and multiple myeloma.

Interventions and comparators

In all studies, rasburicase was administered for the treatment or prophylaxis of hyperuricemia[11,13,14] or TLS.[9,10,12,15] In the RCT, three treatment groups were compared: rasburicase at 0.20 mg/kg/day for 5 days; rasburicase at 0.20 mg/kg on days 1 to 3, followed by allopurinol at 300 mg/day on days 3 to 5 (both treatments were administered on day 3); and allopurinol at 300 mg/day for 5 days. All of the other studies only examined the effect of rasburicase in patients with no comparators. Rasburicase was administered at 0.20 mg/kg/day for 1 to 7 days in three prospective studies[10,11,13] and for 3 to 7 days in one prospective study.[12] In one retrospective study, rasburicase was administered as a single dose of 3 mg, irrespective of patient weight.[14] In the other retrospective study, patients were administered various low doses of rasburicase with a median overall dose of 3 mg.[15] Concomitant hydration was given to patients in the RCT[9] and one retrospective study.[12] Supportive therapy, including hydration, urinary alkalinization, and allopurinol was given to patients in one retrospective study as needed.[14]

Outcomes measured

In all studies, serum uric acid levels were analyzed at baseline and subsequent to rasburicase treatment. A uric acid response to rasburicase treatment was defined as achieving a serum level of ≤7.5 mg/dL in two studies,[9,11] and as the normalization of serum levels after 3 days of treatment in one study.[12] Creatinine levels were measured at baseline and after treatment in four studies.[10,12,14,15] Patient that experienced renal failure or required renal replacement therapy was reported in all studies. Adverse events related to the administration of rasburicase were reported in four studies.[9-11,13]

Summary of Critical Appraisal

Details on critical appraisal can be found in Appendix 4.

The sample size of the studies ranged from 45 to 387 adult patients, with three studies enrolling a small number of patients (≤100). The method of randomization was described in the RCT, but both patient and outcome assessors were not blinded to treatment.[9] In all of the prospective studies, no randomization or blinding was employed and the length of rasburicase treatment varied within studies depending on patient needs.[10-13] In the RCT,[9] one prospective study,[12] and the retrospective studies,[14,15] rasburicase treatment was administered with concomitant

hydration, another treatment for hyperuricemia and TLS. Outcomes were clearly defined in the RCT,[9] two prospective studies,[11,13] and one retrospective study[14] where the range of normal uric acid or creatinine levels were stated.

In two prospective studies, the samples were taken from multiple centers or countries, which would be reflective of a broader range of patients seen in practice.[11,12] The retrospective studies analyzed patients that reflected clinical practice, as the patients had impairment of renal function and comorbidities.[14,15]

Summary of Findings

Details on study findings can be found in Appendix 5.

What is the evidence for the clinical effectiveness of rasburicase for adults with acute tumor lysis syndrome to reduce or eliminate the need for hemodialysis?

In the RCT, the treatment group administered rasburicase at 0.20 mg/kg/day for 5 days was found to have a statistically significantly greater uric acid response rate (≤7.5 mg/dL) than the group administered allopurinol at 300 mg/day for 5 days (P=0.001).[9] This difference was also seen in the subgroup of patients at high risk of TLS and in the subgroup of patients who had baseline hyperuricemia. The treatment group administered rasburicase for 3 days and allopurinol for 3 days also exhibited a greater uric acid response rate, but this difference was not statistically significant. The proportion of patients whose serum creatinine levels (a measure of kidney function) increased to >1.4 mg/dL was evenly distributed between treatment groups. The percentage of patients who experienced acute renal failure was 2% in the rasburicase and allopurinol groups, and 5% in the rasburicase plus allopurinol group. The need for hemodialysis was not reported in this study.

In the prospective studies, the administration of rasburicase at 0.20 mg/kg/day for up to 7 days was found to effectively lower plasma uric acid levels.[10-13] In three studies, the uric acid response rate was 100%, where all patients attained normal uric acid levels after rasburicase treatment.[10,11,13] Similarly, all patients who were treated for at least three days were found to attain normal uric acid levels in the other prospective study.[12] Creatinine levels decreased with rasburicase treatment in two studies.[10,12] No patients required dialysis for renal failure in two prospective studies.[10,12] One patient underwent dialysis for acute renal failure despite reduced uric acid levels with rasburicase in the international compassionate use study.[11] In the North American compassionate use trial, 28 adults (7.2%) experienced acute renal insufficiency and 20 adults (5.2%) underwent hemodialysis.[13]

In one retrospective study, plasma uric acid levels were restored to normal (≤7 mg/dL) in 72% of the patients after a single dose of 3 mg rasburicase and those that did not achieve normal levels had significantly higher baseline uric acid levels.[14] Similarly, another retrospective study found that patients who were unable to achieve a plasma uric acid level of <475.8 µmol/L (5.4 mg/dL) after low dose rasburicase treatment had a statistically significantly higher baseline uric acid level than patients who were able to achieve this level.[15] Creatinine levels were reported to decrease slightly 24 hours after rasburicase administration in one retrospective study,[14] and within 7 days in patients with elevated baseline creatinine in the other study.[15] No patients with elevated baseline creatinine levels were on dialysis at the time of rasburicase administration or required renal replacement therapy during follow-up in one study.[15] The other retrospective

study found that in 28% of rasburicase treatment episodes, the patient experienced renal failure (serum creatinine >2.5 mg/dL), with 77% of these patients having acute renal failure.[14] Of the patients who experienced acute renal failure, 44% required newly initiated dialysis.[14]

What is the evidence for the safety of rasburicase for adults with acute tumor lysis syndrome?

In the RCT, there were few drug-related adverse events in the rasburicase group (4%), rasburicase plus allopurinol group (5%), and allopurinol group (1%).[9] More patients withdrew due to adverse events in the rasburicase plus allopurinol group (5%) than in the rasburicase (1%) and allopurinol (2%) groups. Drug-related hypersensitivity reactions were reported in 4% of patients in the rasburicase group and 1% of patients in the rasburicase plus allopurinol group. These reactions included arthralgia, myalgia, rash, peripheral edema, and severe (grade 3) hypersensitivity.

In one prospective study, of a total of 163 rasburicase doses administered, one adult patient experienced grade 1 vomiting.[10] In another prospective study, the most common drug-related adverse events reported were headache, fever, and rigors, and these events occurred in less than 2% of patients.[11] Rasburicase treatment was stopped before 3 days in 3 patients due to an increase in liver enzymes in the international compassionate use study, but this effect was reversible upon treatment withdrawal.[12] In the North American compassionate use trial, the most common drug-related events were headache, rash, fever, and vomiting, and these events occurred in less than 2% of patients.[13] In this trial, two adults experienced a single episode each of grade 3 (severe) toxicity, and no adults experienced grade 4 (life threatening) toxicity.[13]

Of the retrospective studies, there was one documented case of methemoglobinemia in one study[15] and no reported adverse events in the other study.[15] No deaths associated with rasburicase were reported in any study.

What is the evidence for the cost effectiveness of rasburicase compared with allopurinol or hydration for adults with acute tumor lysis syndrome to reduce or eliminate the need for hemodialysis?

No evidence on the cost effectiveness of rasburicase compared with allopurinol or hydration for adults with acute TLS was identified.

Limitations

There was one included RCT, while the other studies were generally of lower quality design, with no randomization or blinding. In the non-RCT studies, there were no comparators used and a pre-post comparison was employed, which is less informative to determine whether rasburicase treatment decreases the need for hemodialysis. In pre-post studies, potential confounding variables may differ in the pre-intervention and post-intervention time periods. In the included studies, this may have been changes to standard treatment or other hospital practices that may influence outcomes. Similarly, the included studies reported great detail on changes in uric acid and creatinine levels, but did not focus on the need for hemodialysis for renal failure in patients. It was also unclear how long patients were followed for after treatment, and renal failure may have occurred after study analysis.

Rasburicase treatment doses and length of treatment varied between studies, making it difficult to compare results. In addition, a few studies administered concomitant hydration therapy, which may have contributed to the positive effect seen with rasburicase with regards to uric acid and creatinine levels. The types of cancers of enrolled patients varied between studies, which makes it difficult to generalize results.

No evidence on the cost effectiveness of rasburicase compared with allopurinol or hydration for adults with acute TLS was identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The pathophysiology and clinical consequences of TLS has been discussed less frequently in the context of adult patient populations despite adults being more likely to experience complications from TLS due to comorbidities.[16] There has been a greater body of evidence for the use of rasburicase in pediatric patients, which resulted in its earlier approval by the Food and Drug Administration (FDA) for this patient population in 2002.[4] In this review, rasburicase was found to be effective in reducing hyperuricemia in adult cancer patients at risk for developing TLS by rapidly reducing plasma uric acid levels. One phase III RCT found that rasburicase was superior to allopurinol in preventing hyperuricemia in adult leukemia and lymphoma patients at high risk of TLS.[9]

Rasburicase was generally well tolerated, with few reported adverse events. Furthermore, few patients required hemodialysis for acute renal failure in the included studies. Methemoglobinemia, a known adverse effect of rasburicase, was reported in one patient in one study.[14] The North American compassionate use study found that few adult patients experienced grade 3 toxicity and no adult patients experienced grade 4 toxicity.[13]

According to the FDA, the recommended dosage of rasburicase is 0.20 mg/kg/day for up to 5 days in adult patients.[17] This dosage regimen was based on the clinical studies that led to the FDA approval of rasburicase in 2009 for the management and treatment of hyperuricemia in adult cancer patients, one of which was included in this review.[9] Various studies, including those in this review, have shown that rasburicase can be effective when administered at lower doses and for shorter durations, which may decrease treatment costs.

No evidence on the cost effectiveness of rasburicase compared with allopurinol or hydration for adults with acute TLS was identified.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Tazi I, Nafl H, Elhoudzi J, Mahmal L, Harif M. Management of pediatric tumor lysis syndrome. Arab J Nephrol Transplant. 2011 Sep;4(3):147-54.

2. Pession A, Melchionda F, Castellini C. Pitfalls, prevention, and treatment of hyperuricemia during tumor lysis syndrome in the era of rasburicase (recombinant urate oxidase). Biologics [Internet]. 2008 Mar [cited 2013 Feb 25];2(1):129-41. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727789

3. Larson RA, Pui CH. Tumor lysis syndrome: definition, pathogenesis, clinical manifestations, etiology and risk factors. 2012 Mar 1 [cited 2013 Mar 13]. In: UpToDate [Internet]. Version 21.1. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.

4. Malaguarnera G, Giordano M, Malaguarnera M. Rasburicase for the treatment of tumor lysis in hematological malignancies. Expert Rev Hematol. 2012 Feb;5(1):27-38.

5. Bose P, Qubaiah O. A review of tumour lysis syndrome with targeted therapies and the role of rasburicase. J Clin Pharm Ther. 2011 Jun;36(3):299-326.

6. Larson RA, Pui CH. Tumor lysis syndrome: prevention and treatment. 2013 Feb 12 [cited 2013 Mar 13]. In: UpToDate [Internet]. Version 21.1. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.

7. Fasturtec® (rasburicase) powder for injection: 1.5 mg/vial [product monograph] [Internet]. Laval (QC): Sanofi-aventis Canada Inc; 2007 Feb 9. [cited 2013 Feb 8]. Available from: http://products.sanofi.ca/en/fasturtec.pdf

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2013 Jan 10];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

9. Cortes J, Moore JO, Maziarz RT, Wetzler M, Craig M, Matous J, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study. J Clin Oncol. 2010 Sep 20;28(27):4207-13.

10. Wang LY, Shih LY, Chang H, Jou ST, Lin KH, Yeh TC, et al. Recombinant urate oxidase (rasburicase) for the prevention and treatment of tumor lysis syndrome in patients with hematologic malignancies. Acta Haematol. 2006;115(1-2):35-8.

11. Bosly A, Sonet A, Pinkerton CR, McCowage G, Bron D, Sanz MA, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer. 2003 Sep 1;98(5):1048-54.

12. Coiffier B, Mounier N, Bologna S, Ferme C, Tilly H, Sonet A, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol [Internet]. 2003 Dec 1 [cited 2013 Mar 6];21(23):4402-6. Available from: http://jco.ascopubs.org/content/21/23/4402.full.pdf+html

13. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia. 2005 Jan;19(1):34-8.

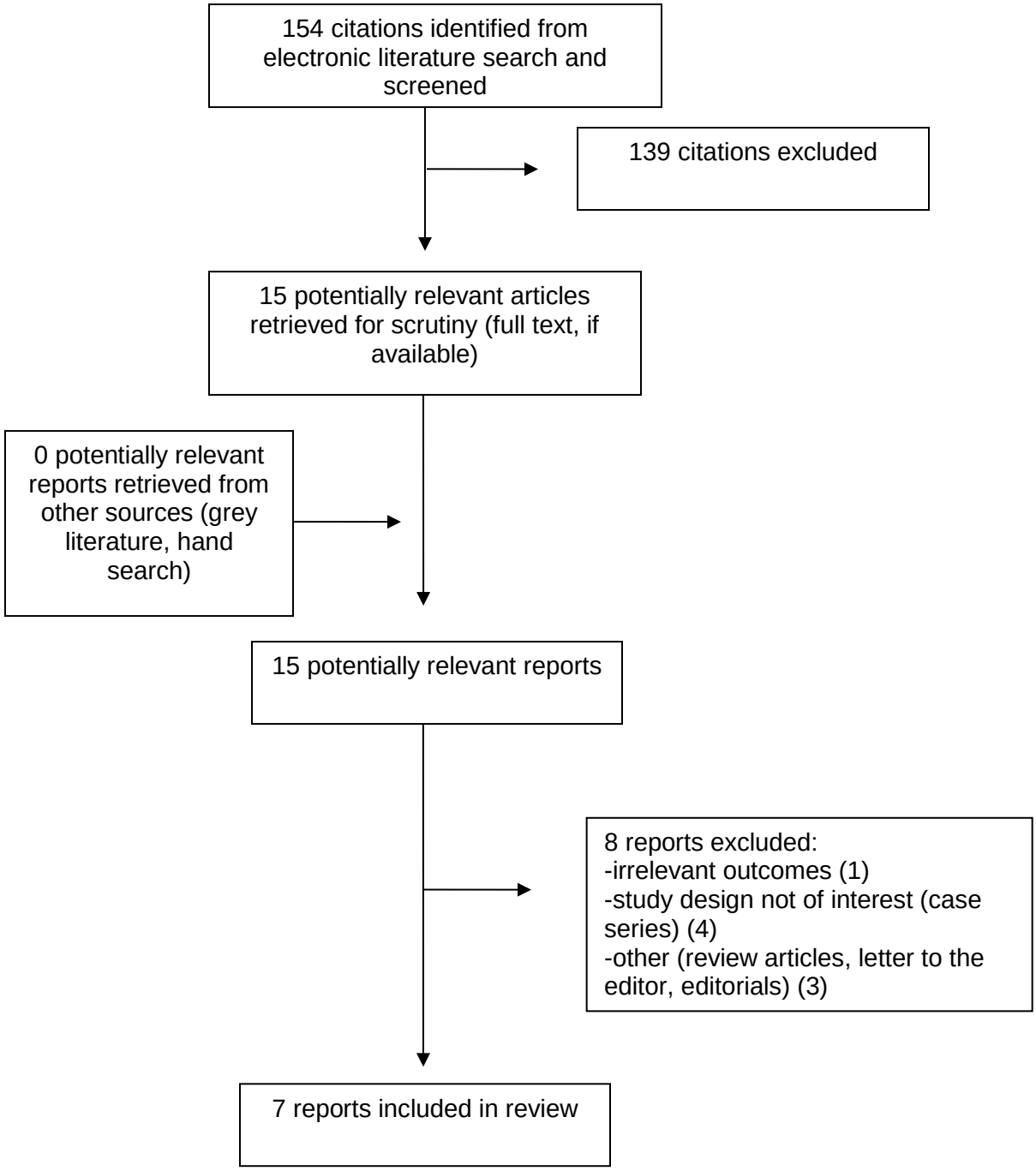
14. Trifilio SM, Pi J, Zook J, Golf M, Coyle K, Greenberg D, et al. Effectiveness of a single 3-mg rasburicase dose for the management of hyperuricemia in patients with hematological malignancies. Bone Marrow Transplant. 2011;46(6):800-5.

15. Hummel M, Reiter S, Adam K, Hehlmann R, Buchheidt D. Effective treatment and prophylaxis of hyperuricemia and impaired renal function in tumor lysis syndrome with low doses of rasburicase. Eur J Haematol. 2008 Apr;80(4):331-6.

16. Seiter KP, Sarlis NJ, Kim ES. Management of hyperuricemia in adults with or at risk of tumor lysis syndrome. Community Oncol. 2011;8(4):163-70.

17. Kennedy LD, Koontz S, Rao K. Emerging role of rasburicase in the management of increased plasma uric acid levels in patients with hematologic malignancies. J Blood Med [Internet]. 2011 [cited 2013 Feb 25];2:1-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262356

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Case Studies, Case Series, Hospital Experiences

Efficacy of rasburicase in adults

18. Chao CT, Chiang CK. Rasburicase for huge hepatocellular carcinoma with tumor lysis syndrome: case report. Med Princ Pract. 2012;21(5):498-500.
PubMed: PM22687814

19. Hooman N, Otukesh H. Single dose of rasburicase for treatment of hyperuricemia in acute kidney injury: a report of 3 cases. Iran J Kidney Dis. 2011 Mar;5(2):130-2.
PubMed: PM21368393

20. Calvo-Villas JM, Urcuyo BM, Umpierrez AM, Sicilia F. Acute tumor lysis syndrome during oral fludarabine treatment for chronic lymphocytic leukemia. Role of treatment with rasburicase. Onkologie. 2008 Apr;31(4):197-9.
PubMed: PM18418022

21. Ho VQ, Wetzstein GA, Patterson SG, Bradbury R. Abbreviated rasburicase dosing for the prevention and treatment of hyperuricemia in adults at risk for tumor lysis syndrome. Support Cancer Ther. 2006 Apr 1;3(3):178-82.
PubMed: PM18632493

22. McDonnell AM, Lenz KL, Frei-Lahr DA, Hayslip J, Hall PD. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. Pharmacotherapy. 2006 Jun;26(6):806-12.
PubMed: PM16716134

Safety of rasburicase in adults

23. Browning LA, Kruse JA. Hemolysis and methemoglobinemia secondary to rasburicase administration. Ann Pharmacother. 2005 Nov;39(11):1932-5.
PubMed: PM16204390

24. Pitini V, Bramanti P, Arrigo C, Sessa E, La GG, Amata C. Acute neurotoxicity as a serious adverse event related to rasburicase in a non-Hodgkin's lymphoma patient. Ann Oncol. 2004;15(9):1446.
PubMed: PM15319256

APPENDIX 3: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention and Comparator	Clinical Outcomes Measured
Cortes[9] 2010 USA	Open-label, parallel group RCT	275 patients with active leukemia or lymphoma at high or potential risk for TLS (hyperuricemia, aggressive disease, LDH≥2x upper limit of normal) undergoing cytoreductive chemotherapy – mean age 57 ± 16 years, 63% male	Rasburicase 0.20 mg/kg/day for 5 days (n=92) Rasburicase 0.20 mg/kg/day days 1-3 + Allopurinol 300 mg/day days 3-5 (n=92) Allopurinol 300 mg/day for 5 days (n=91) All drugs were administered before or during the first cycle of chemotherapy All but 4 patients received hydration during the study	Plasma uric acid response (≤7.5 mg/dL days 3-7), safety
Wang[10] 2006 Taiwan	Prospective observational study Multicenter July 2003-July 2004	45 patients with ALL or multiple myeloma at risk for TLS before or during the initiation of chemotherapy (uric acid level ≥8 mg/dL) – 18 children and 27 adults (median age 59.3, 67% male)	Rasburicase 0.20 mg/kg/day for 1-7 days depending on individual's needs, given the day before or the day chemotherapy begin	Uric acid levels, creatinine levels, renal function, safety
Jeha[13] 2005 North America	Prospective observational study – compassionate use trial Multicenter (39 in USA, 2 in Canada) Jan 1999-Sept 2002	1069 patients with hematologic malignancies or solid tumours (most patients had a high tumour burden and elevated LDH levels) – 682 pediatric patients and 387 adult patients (median age 54 years, range 18-90, 69% male)	Rasburicase 0.20 mg/kg/day for 1-7 days administered prophylactically or to treat hyperuricemia	Uric acid levels, renal function, safety
Bosly[11] 2003 Multinational (Australia, Europe, Asia)	Prospective observational study – compassionate use trial Jan 1999-Dec 2001	278 patients with cancer (lymphomas and leukemias) who presented with or were at significant risk for hyperuricemia (most patients had a high tumour burden and elevated LDH levels) – 166 pediatric patients and 112 adult patients (median age 54 years, range 18-80, 69% male)	Rasburicase 0.20 mg/kg/day for 1-7 days depending on individual's needs	Uric acid levels (normal levels ≤7.5 mg/dL), safety
Coiffier[12]	Prospective	100 patients with	Rasburicase	Uric acid levels

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention and Comparator	Clinical Outcomes Measured
2003 France	observational study – single-arm, open-label Multicenter May 2001-June 2002	previously untreated aggressive non-Hodgkin's lymphoma at risk of TLS during the induction phase of chemotherapy (tumour volume ≥5 cm, LDH and/or uric acid level above normal upper limits, increase in creatinine levels) – median age 57 years (range 25-85), 64% male	0.20 mg/kg/day for 3-7 days starting before induction chemotherapy or on the same day (depending on risk of TLS) +Hydration	(response defined as normalization of uric acid after 3 days of treatment maintained throughout chemotherapy), creatinine levels
Trifilio[14] 2011 USA (single center)	Retrospective study Single-center June 2003-Jan 2008	247 patients with hematological malignancies (myeloma, NHL, ALL, CLL) and uric acid level >7 mg/dL who received an initial 3 mg dose of rasburicase for hyperuricemia (287 treatments) – median age 62 years (range 20-92)	Rasburicase, single dose of 3 mg +supportive therapy as needed (hydration, urinary alkalinization, allopurinol)	Uric acid levels (normal levels ≤7 mg/dL), serum creatinine levels (renal failure >2.5 mg/dL)
Hummel[15] 2008 Germany	Retrospective study Single-center Jan 2002-July 2006	50 consecutive cancer patients (ALL, AML, CLL, CMPD, NHL) treated with rasburicase for clinical or laboratory TLS (n=42) or for the prophylaxis of TLS (n=8) – median age 67 years (range 16-88), 58% male	Rasburicase, various doses (median overall dose 3 mg) + IV hydration	Uric acid level within 24 hours after first dose, creatinine levels

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; CMPD=chronic myeloproliferative disease; NHL=non-Hodgkin's lymphoma; LDH=lactate dehydrogenase; RCT=randomized controlled trial; TLS=tumour lysis syndrome

APPENDIX 4: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Randomized controlled trial		
Cortes[9] 2010	• Method of randomization described • Outcome measures clearly defined • Losses to follow up described • Sample taken from multiple centers	• Patient and outcome assessors not blinded • No power calculation was performed to determine sample size • Treatments were administered with concomitant hydration
Prospective studies		
Wang[10] 2006	• Prospective study • Objective and intervention clearly described • Sample taken from multiple centers	• No randomization or blinding • Small sample size (n=27 adults) • Study was conducted in Taiwan, which may limit generalizability to other countries • Varying lengths of rasburicase treatment • Outcomes not clearly defined (normal uric acid range, normal creatinine range)
Jeha[13] 2005	• Prospective study • Sample taken from multiple countries and is representative of population of interest • Outcome measures clearly described	• No randomization or blinding • Varying lengths of rasburicase treatment
Bosly[11] 2003	• Prospective study • Sample taken from multiple countries and is representative of population of interest • Outcome measures clearly described	• No randomization or blinding • Varying lengths of rasburicase treatment • No separate reporting of safety data in adult and pediatric patients
Coiffier[12] 2003	• Prospective study • Sample taken from multiple countries and is representative of population of interest	• No randomization or blinding • Varying lengths of rasburicase treatment • Rasburicase was administered with hydration • Outcomes not clearly defined
Retrospective studies		
Trifilio[14] 2011	• Study reflected clinical practice, patients were elderly with comorbidities • Outcome measures clearly described	• Retrospective analysis • Single institution study • No randomization or blinding • Supportive therapy (hydration, alkalinization, allopurinol) was administered as needed
Hummel[15] 2008	• Study reflected clinical practice, patients had high uric acid levels and impairment of renal function	• Retrospective analysis • Small sample size (N=50) • Varying doses of rasburicase administrated • Rasburicase was administered with hydration • Outcomes not clearly defined (normal uric acid range, normal creatinine range)

APPENDIX 5: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Randomized controlled trial		
Cortes[9] 2010	Plasma uric acid response rate, % (95% CI) Rasburicase: 87 (80-94) Rasburicase+Allopurinol: 78 (70-87) Allopurinol: 66 (56-76) Rasburicase>Allopurinol (P=0.001) Uric acid concentrations were rapidly reduced by hour 4 in the Rasburicase and Rasburicase+Allopurinol groups. Plasma uric acid response rate in patients at high risk of TLS, % (95% CI) Rasburicase: 89 Rasburicase+Allopurinol: 79 Allopurinol: 68 Rasburicase>Allopurinol (P=0.001) Plasma uric acid response rate in patients with baseline hyperuricemia, % (95% CI) Rasburicase: 90 Rasburicase+Allopurinol: 77 Allopurinol: 53 Rasburicase>Allopurinol (P=0.015) Drug-related adverse events, % Rasburicase: 4 Rasburicase+Allopurinol: 5 Allopurinol: 1 Most common AEs: blood and lymphatic system, general disorders and administration site conditions, GI system Drug-related hypersensitivity reaction, % Rasburicase: 4 (arthralgia, myalgia, rash, peripheral edema, grade 3 hypersensitivity) Rasburicase+Allopurinol: 1 (rash, grade 3 hypersensitivity) Allopurinol: 0 Withdrawal due to adverse events, n Rasburicase: 1 (hyperbilirubinemia and neutropenic sepsis) Rasburicase+Allopurinol: 5 Allopurinol: 2 (TLS) Clinical TLS, % Rasburicase: 3 Rasburicase+Allopurinol: 3 Allopurinol: 4 All considered unrelated to study medication Laboratory TLS, % Rasburicase: 21 Rasburicase+Allopurinol: 27	"In this study, rasburicase generally was well tolerated and no new safety concerns for adult patients were identified…No major differences in the frequencies of AEs, treatment-related AEs, serious AEs, treatment discontinuations due to AEs, and deaths were observed between rasburicase and allopurinol groups…In summary, rasburicase has a more favorable risk-benefit ratio than allopurinol for the initial management of uric acid plasma concentrations in adult patients with hematologic malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid." (p. 4212)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Allopurinol: 41 Rasburicase versus Allopurinol: P=0.003 R+A versus Allopurinol: P=0.054 <u>Increased blood creatinine (>1.4 mg/dL), %</u> Rasburicase: 8 Rasburicase+Allopurinol: 10 Allopurinol: 10 <u>Renal failure/impairment, %</u> Rasburicase: 4 Rasburicase+Allopurinol: 9 Allopurinol: 2 <u>Acute renal failure, %</u> Rasburicase: 2 Rasburicase+Allopurinol: 5 Allopurinol: 2	
Prospective studies		
Wang[10] 2006	Adults (n=27) received a median of 4 days of rasburicase treatment. Uric acid levels declined from a median of 10.8 mg/dL to 0.5 mg/dL, indicating a 100% response rate (lowering uric acid to normal levels) to rasburicase. Creatinine levels declined from a median of 3.1 mg/dL (range 1.9-7.0) to 2.7 mg/dL (range 1.6-6.6). Renal dysfunction was present in 7 patients prior to chemotherapy and rasburicase treatment. No patients required dialysis for renal failure during chemotherapy treatment. Of a total of 163 doses administered, one adult experienced grade 1 vomiting.	"Our study confirms the results of other investigators, demonstrating the efficacy and safety of rasburicase in controlling hyperuricemia and preventing tumor lysis syndrome in both pediatric and adult patients. Although rasburicase is expensive, the low incidence of renal failure and of adverse effects in patients treated with it suggests that it may be a cost-effective way of reducing the complications of tumor lysis syndrome." (p. 38)
Jeha[13] 2005	Hyperuricemia was defined as uric acid levels above the upper limit of normal for age and sex. <u>Efficacy</u> There was a significant decline in uric acid levels (P<0.001) in 212/212 (100%) of adult patients who were hyperuricemic at baseline and all 126/126 (100%) adult patients who were nonhyperuricemic as baseline. <u>Hemodialysis</u> Acute renal insufficiency developed during the study in 28 adults (7.2%). In total, 20 (5.2%) adults underwent hemodialysis. <u>Drug-related adverse events in adult patients after one course of treatment, n (%)</u> Grade 1: 11 (2.8) Grade 2: 5 (1.3)	"The results of this large compassionate use study in over 1000 patients confirms the safety of rasburicase and provides further evidence of its efficacy in the prevention and treatment of hyperuricemia in adults and children undergoing chemotherapy for cancer." (p. 38)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Grade 3: 2 (0.5) Grade 4: 0 The most frequent adverse reactions in the total population (adults and children) were headache (0.7%), rash (0.4%), fever (0.3%) and vomiting (0.3%). No on-study deaths were considered related to rasburicase treatment.	
Bosly[11] 2003	Efficacy 97 adult patients were included in the efficacy analysis. The median plasma uric acid level decreased from 13.1 mg/dL to 0.3 mg/dL in adults presenting with hyperuricemia. The median uric acid level decreased from 4.9 mg/dL to 0.3 mg/mL in adults presenting with normal uric acid levels. All patients had uric acid levels within the normal range after rasburicase treatment (response rate 100%). Hemodialysis One adult patient underwent dialysis for acute renal failure despite reduction of uric acid levels to normal values with rasburicase. Safety Safety analyses were performed on both pediatric and adult patients combined. The most common drug-related adverse events were: headache (1.8%), fever (1.4%), rigors (1.1%). 19 patients died during the study, most commonly from disease progression and sepsis, not attributable to rasburicase.	"In both the prophylaxis and treatment populations, the reduction in plasma uric acid levels was quite similar for adults and children…Rasburicase was well tolerated, with mild headache being the most common side effect..a limited number of patients required dialysis despite experiencing a reduction in plasma uric acid levels to normal values." (p. 1053)
Coiffier[12] 2003	Efficacy All of the 95/100 patients treated for at least 3 days with 0.20 mg/kg rasburicase responded to treatment. Uric acid levels decreased within the first 4 hours after administration of rasburicase and were maintained throughout treatment in all patients. Creatinine levels decreased during rasburicase treatment. No patient had an increase in creatinine level or required dialysis. Safety Rasburicase treatment was stopped before 3 days in 3 patients due to an increase in liver enzymes, but this was reversible within a few days in these patients without sequelae. Liver toxicity was considered by investigators to be related to rasburicase or to chemotherapy.	"Our study demonstrated that rasburicase is also a highly effective, fast acting, and reliable uricolytic agent for adult patients with aggressive lymphoma. Plasma uric acid levels were controlled in all patients who received rasburicase, including the 11 hyperuricemic patients at baseline…Renal function was preserved, which is of paramount importance in the management of these patients and for the prevention of many complications of chemotherapy." (p. 4405-4406)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Retrospective studies		
Trifilio[14] 2011	287 treatment episodes (in 247 patients) <u>Patients with uric acid restored to normal levels after 3 mg rasburicase, n (%)</u> Uric acid ≤7 mg/dL: 206 (72) Uric acid ≤5 mg/dL: 137 (48) The baseline uric acid levels of patients who achieved normal levels after rasburicase was significantly lower (P<0.0001) than the uric acid levels of patients who did not achieve normal levels after rasburicase. 6 (14%) patients required a second dose (3 mg or 1.5 mg) to restore normal uric acid levels. <u>Median serum creatinine levels, mg/dL (range)</u> Baseline: 1.7 (0.6-937) 24-hours: 1.6 (0.6-8.7) 24-hour absolute change: -0.1 (-3.3 to +1.4) <u>Patients experience renal failure (serum creatinine >2.5 mg/dL), n (%)</u> Acute: 62 (77) Chronic: 19 (23) Of patients experiencing acute renal failure (n=62), 27 (44%) underwent newly initiated dialysis. There were 82 (29%) patients who exhibited clinical evidence of TLS. There was one documented case of methemoglobinemia.	"Our data demonstrate the effectiveness of a single low dose of rasburicase in lowering serum uric acid levels in patients with hematological malignancies…Renal function remained stable early after therapy and improved over the subsequent week." (p. 803)
Hummel[15] 2008	<u>Dose of rasburicase, mg (mg/kg)</u> Prophylaxis group (n=8): 3.75 (0.056) Treatment group (n=42): 3 (0.044) This study used a uric acid level of 475.8 µmol/L (5.4 mg/dL) as a divide. Patients who had a uric acid level of >475.8 µmol/L after rasburicase treatment had a statistically significantly higher uric acid level before treatment than patients who achieved a uric acid level of <475.8 µmol/L (P=0.0270). Baseline creatinine was elevated in 42 patients. In this subgroup, median creatinine levels decreased from 206 to 118.5 µmol/L within 7 days after rasburicase administration. No patients in this subgroup were on dialysis at the time of rasburicase administration. No patients required renal replacement therapy. No adverse events occurred in this study.	"This is the first study to demonstrate the efficacy of low doses of rasburicase for prophylaxis and treatment of TLS in a patient cohort with markedly elevated serum uric acid levels and a large proportion of patients with impaired renal function. Our data support the use of rasburicase at lower doses than recommended by the manufacturer for prophylaxis and treatment of TLS." (p. 335)

AE=adverse event; TLS=tumour lysis syndrome