RASBURICASE INDUCED METHEMOGLOBINEMIA: A SYSTEMATIC REVIEW OF DESCRIPTIVE STUDIES

Abstract

Purpose: There is an increased number of reports being published on rasburicase-induced methemoglobinemia recently. We aimed to identify and critically evaluate all the descriptive studies that described the rasburicase-induced methemoglobinemia, its treatment approach, and their outcomes.

Methodology: PubMed and grey literature databases were searched from inception to January 2021 using search terms “rasburicase” and “methemoglobinemia” without any language and date restriction. A bibliographic search was also done to find additional studies. Only descriptive studies on Rasburicase-induced methemoglobinemia were included for our review. Two contributors worked independently on study selection, data abstraction, and quality assessment, and any disagreements were resolved by consensus or discussion with a third reviewer.

Result: A total of 22 reports including 25 patients (21 male, 3 female patients, and 1 study did not specify the gender of the patient) aged from 6 to 75 years were included in the review. Immediate withdrawal of the drug and administering methylene blue, ascorbic acid, blood transfusion, and supportive oxygen therapy are the cornerstone in the management of rasburicase-induced methemoglobinemia.

Conclusion: Rasburicase administration should be followed by careful monitoring of patients for any severe complication and treat it as early as possible appropriately. In a patient who

presents with rasburicase-induced haemolysis or methemoglobinemia, it is often important to expect a diagnosis of G6PD deficiency unless otherwise confirmed and to avoid administering methylene blue, even though the patient is from a low-risk ethnicity for G6PDD.

Review criteria: how did you gather the information you considered in your review?

The comprehensive search strategy was conducted using PubMed databases. Additional studies were also identified using citation search of included studies, Google Scholar, Grey literature, and ResearchGate. The studies which reported methemoglobinemia followed by the rasburicase administration were included in this review. The study screening and data extractions were conducted by two independent reviewers any discrepancies were resolved by the third reviewer. The required data such as patient's demographic details, study characteristics, diagnostic characteristics, management, and outcomes were extracted. All the data were summarised in this review.

Message for the clinic: what is the 'take-home' message for the clinician?

The main intention of this systematic review is to create awareness to all rasburicase prescribing clinicians about the potential adverse effect not only confined to African American ethnicity but can occur to other ethnicities. It is critical to be aware of non-classical presentations such as methemoglobinemia to ensure timely intervention. This review tries to critically evaluate, synthesize and describe all the data related to methemoglobinemia induced by rasburicase.

Introduction

The US Food and Drug Administration (FDA) has approved Rasburicase Intravenous infusion (Elitek, Sanofi-Aventis US, Inc.) on October 21, 2009, as an indication for the initial management of increased plasma uric acid (PUA) level in patients who are receiving anticancer therapy for leukaemia, lymphoma, and solid tumour malignancies and who are expected to have tumour lysis and subsequent elevation of PUA levels.

A combination of biochemical disorders/metabolic abnormalities arising from either spontaneous or chemotherapy-induced death of tumour cells is tumour lysis syndrome (TLS). Cytotoxicity of the tumour releases intracellular content into the systemic bloodstream, including nucleic acids, proteins, and electrolytes, and may result in the development of hyperuricaemia, hypophosphatemia, hypocalcaemia, and hyperkalaemia. Clinically, this will result in multi-organ effects such as acute kidney injury (AKI), cardiac arrhythmias, and seizures. TLS is the most common oncology emergency, and morbidity and mortality are high without timely detection and early clinical intervention[1]. It is also an anticipated complication of hematologic malignancies from the initiation of cytotoxic chemotherapy but can occur spontaneously as well. TLS can be identified if the laboratory findings meet the Cairo-Bishop criteria of tumour lysis syndrome. According to this criteria, the laboratory tumour lysis syndrome(LTLS) is described if uric acid ≥476 lmol/l or 25% increase from baseline, Potassium ≥ 6.0mmol/l or 25% increase from baseline, Phosphorous ≥2.1 mmol/l (children), ≥1.45 mmol/l (adults) or 25% increase from baseline, Calcium ≤1.75 mmol/l or 25% decrease from baseline and the clinical tumour lysis syndrome is defined if Creatinine ≥ 1.5 ULN (age >12 years or age-adjusted), Cardiac arrhythmia/sudden death and seizure[2].

The treatment of TLS includes clinical management of hyperkalaemia (Insulin/glucose, inhaled beta-agonist, sodium bicarbonate, dialysis, K-binding resins, calcium gluconate), Hyperphosphatemia (Dialysis, phosphate binders), Hypocalcaemia (Calcium gluconate), and Hyperuricemia (dialysis, hydration, alkalization of urine, xanthine oxidase inhibitors like allopurinol, urate oxidase-like rasburicase)[3]. Patients treated with Rasburicase for hyperuricemia caused due to TLS may develop Haemolytic anaemia/haemolysis and methemoglobinemia[4]. Rasburicase, which is a recombinant urate oxidase enzyme, is usually offered to patients who continue to produce TLS. Urate oxidase converts uric acid to allantoin, which is water-soluble and can then be easily excreted in the urine[5]. The detailed pharmacokinetic parameters of rasburicase are shown in Table 1[6].

Table 1: Pharmacokinetic parameters of Rasburicase

Methemoglobinemia is a condition in which methaemoglobin levels will be elevated in the blood. Methaemoglobin is abnormal haemoglobin in which iron molecule in the ferrous form(Fe^{2+}) gets oxidized to ferric form(Fe^{3+})[7]. This reaction impairs haemoglobin's capacity to transport oxygen and carbon dioxide, resulting in tissue hypoxemia and mortality in extreme cases. Symptoms are proportional to the fraction of methaemoglobin. A normal methaemoglobin fraction is about 1% (ranges between 0-3%). The following symptoms are associated with higher levels of methemoglobin:3-15% slight discoloration (e.g., pale, grey, blue) of the skin, 15-20% cyanosis, though patients may be relatively asymptomatic, 25-50% headache, dyspnoea, light-headedness (even syncope), weakness, confusion, palpitations, chest pain, 50-70% abnormal cardiac rhythms; altered mental status, delirium, seizures, coma; profound acidosis, >70% - usually, death.

As a consequence of elevated oxidative stress within the erythrocyte, Rasburicase has been reported to cause both methemoglobinemia and haemolytic anaemia, usually in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Methylene blue is widely used to treat methemoglobinemia as it catalyses one of the reactions that reduce methaemoglobin to haemoglobin. This mechanism is inactive in individuals with G6PD deficiency, though, and methylene blue does not catalyse the reaction but instead becomes oxidized itself, raising the oxidative stress on the cell further[5]. There are no systematic reviews available that highlight the methemoglobinemia induced by the rasburicase administration. Therefore, we conducted a systematic literature review to identify and critically evaluate all case reports and case series on rasburicase association with methemoglobinemia, describing its clinical presentation and management.

Methodology

Data sources and searches

From inception to January 2021, the PubMed database was searched using all available search terms for "rasburicase" AND "methemoglobinemia" without any language or date constraints. Appendix 1 displays the comprehensive PubMed search strategy. Additional studies were identified by searching the citations of all included studies and the grey literature database (OpenGrey, GreyNet, Grey Literature Report, and BIOSIS Previews).

Appendix 1: Detailed search strategy in PubMed

Study selection

The title and abstracts of all the retrieved studies were screened as part of the first-pass screening. At this point, only highly irrelevant studies (i.e. methemoglobinemia due to drugs other than rasburicase) according to the criterion were excluded. Selected studies were subjected to full-text screening based on pre-determined criteria. Only the Descriptive studies

(case reports, letter to the editor, short communication, and case series) on patients (adult and paediatric) who experienced methemoglobinemia following the use of rasburicase for the indication such as Gout, suspected or unsuspected TLS were included. Study selection was conducted by two review authors independently, and any disagreements were resolved by consensus or discussion with a third reviewer.

Data extraction and quality assessment

Following consensus among reviewers, all the necessary data was extracted into a standardized data extraction sheet generated in Excel. The studies were identified using the first author's last name and the year of publication. The data extracted includes Study characteristics, demographic details of the patient, diagnostic characteristics, clinical presentation, methemoglobinemia management, and outcomes. The Oxford Criteria, 2011 were used to grade the level of evidence of the included studies.

Oxford level of evidence criteria can be described as follows; a systematic review of randomized control trials as level 1; randomized trial or observational studies with dramatic effect as level 2; non-randomized controlled cohort studies as level 3; case series, case-control studies, or historically controlled studies as level 4 and; mechanically based reasoning as level 5[8]. The tool developed by Murad et al.,[9] in 2018 was used to assess the methodological quality of the included studies. If the study fulfilled the criteria then it was scored as 1 otherwise as 0. The quality evaluation of included studies was done by considering the total score out of 8, the score 6-8 was considered as good, 3-5 as moderate, and less than 3 as poor quality. Two independent authors were involved in the data extraction and quality assessment of the included studies. Any disagreements in all stages of the review process were resolved through discussion or consultation with a third reviewer.

Quantitative analysis

Meta-analysis was not performed due to a lack of quantitative (numerical) data as we only focused on descriptive studies for inclusion. The protocol for this systematic review has been already registered in PROSPERO (CRD42021234132).

Results

Search results

A total of 44 studies were obtained during the search. Only 28 among them were descriptive studies, out of which 22 studies were included (15 case reports, 2 case series, and 5 letters to the editor). All the included studies were published in the English language and we did not find any additional studies after searching through other sources like citation search and Google scholar. A detailed searching process for including the study has been illustrated in Figure 1.

Figure 1: PRISMA flow diagram for study selection

Characteristics of included studies

The review includes studies that occurred in the USA(19), Europe(2), and Australia(1). Among the included studies, 19 studies reported 1 patient each, and 3 studies reported 2 patients each who developed methemoglobinemia followed by rasburicase administration. The majority of patients were previously diagnosed with lymphoma, T-cell or acute lymphoblastic leukaemia, Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, Burkitt's lymphoma, and few were diagnosed with gout, Neuroendocrine tumour, Status epileptics, IgA variant or refractory aggressive multiple myeloma, sporadic adenomatous

polyposis syndrome and metastatic colon cancer, pulmonary sarcoidosis and mycosis fungoides and AIDS[5,10,19–28,11,29,30,12–18](Table 2).

Table 2: Characteristics of the included studies

Level of evidence and quality assessment

The level of evidence was considered as per the Oxford criteria 2011 in which case series was graded as 4 and remaining evidence was graded as 5. The methodological quality assessment of included studies revealed that 19 studies were good (score 6–8), with an average score of 6.10 out of 8, and 3 studies were moderate with the score of 5 each. All the studies provided a very good explanation of the occurrence of the condition, management, and outcome.

Appendix 2: Quality assessment of the included studies

Treatment characteristics

Data from 25 patients (21 male, 3 female patients, and 1 study did not specify the gender of the patient) belonging to race African-American(13), Caucasian(3), and each from Hispanic, mixed Mauritian-Chinese, Laotian and Cambodian race, and the remained studies did not specify the ethnicity of patients. The age of the patients ranged from 6 to 75 years. Patients were administered with 6 mg single dose or 3mg/6mg twice daily up to a single dose of 22.5 mg of rasburicase intravenously for TLS (possible, spontaneous, anticipated, diagnosed, or undiagnosed and which met Cairo Bishop criteria). The patients were also on other concomitant chemotherapeutic drugs. (Table 3)

Table 3: Treatment Characteristics

Diagnostic Characteristics

Patients upon administration of rasburicase due to increased uric acid level (normal range: Adult male: 4.0-8.5 mg/dL or 0.24-0.51 mmol/L. Adult female: 2.7-7.3 mg/dL or 0.16-0.43 mmol/L, Child: 2.5-5.5 mg/dL or 0.12-0.32 mmol/L, New-born: 2.0-6.2 mg/dL) and for suspected or unsuspected TLS started developing dyspnoea, shortness of breath, hypoxia, cyanosis, lethargy, tachypnoea, tachycardia, syncope, and other symptoms within 3 hours to 3 days. This has led to suspect methemoglobinemia induced due to rasburicase administration and the methaemoglobin level in the blood showed a minimum of 5.1% to a maximum of 23% (Normal range:0.06-0.24 g/dL or 9.3-37.2 μmol/L,0.4-1.5% of total haemoglobin, and the possible critical values is > 40% of total haemoglobin)[31].

The laboratory values showed an increased level of WBC, Potassium, Serum creatinine, LDH, Phosphorus, Reticulocyte count, Bilirubin (Direct and total bilirubin), and decreased level of haemoglobin, calcium, haptoglobin, and haematocrit. The peripheral blood smear shows numerous 'blister' cells, few 'bite' cells, Howell–Jolly bodies, occasional schistocytes, burr cells, CLL, irregularly contracted cells, and retraction of haemoglobin from the red cell membrane. Heinz bodies were demonstrated on supravital staining with methylene blue. 15 out of 25 patients were presented with some degree of haemolytic anaemia[5,10,19–28,11,29,30,12–18](Table 4).

Table 4: Diagnostic Characteristics

Management and Outcome

The management of rasburicase-induced methemoglobinemia includes the immediate withdrawal of the rasburicase and administration of methylene blue, ascorbic acid, blood

transfusion, and supportive oxygen therapy. However, the patients who are G6PD deficiency are not administered methylene blue, since it raises the oxidative stress on the cell. Among all the included studies, methylene blue was administered in 8 patients depending on the severity and G6PD deficiency status. In most of the studies, oxygen supplementation and blood transfusion were sufficient to manage the condition. Most of the patients recovered within 24 hrs but a few of them took 4 days whereas one patient took as long as 25 days. Out of 25 patients, 2 patients died during treatment. (Table 5)

Table 5: Management and outcome of the condition

Discussion

Although rasburicase-induced methemoglobinemia is rare, our study discovered the first occurrence in 2005, which occurred in an African American male in the United States. The majority of the cases have occurred in the United States of America. Methemoglobinemia caused by rasburicase is a rare complication, although it is somewhat more frequent in African-Americans, according to our research. Rasburicase is usually prescribed in the case of TLS in chemotherapeutic patients. Following the initiation of cytotoxic chemotherapy or cytolytic antibody therapy, the release of intracellular metabolites such as nucleic acids, proteins, phosphorus, and potassium will disrupt normal homeostatic mechanisms, triggering hyperuricemia, hyperkalaemia, hyperphosphatemia, hypocalcaemia, and uraemia. Uric acid or calcium phosphate crystallization of renal tubules may also affect renal function. The pathogenesis of EBM guidelines supports our review[32].

Many medications, whether used systematically or topically, can cause methemoglobinemia. Drugs that induces methemoglobinemia include Acetaminophen-Phenacetin-Antipyrin,

Phenytoin, Sodium Valproate, Fentanyl, Phenazopyridine Celecoxib, Phenobarbital, Sulphonamide, Phenazopyridine hydrochloride, Flutamide, Chloroquine, Primaquine Phosphate, Quinine, Para-Amino salicylic Acid, Rifampin, Phenelzine, Trazodone, Nitro-glycerine, Piperazine, Isosorbide Dinitrate, Amyl Nitrite, Silver Nitrate, Potassium Permanganate, Nitrate Salt, Benzocaine, Sodium Nitrate, Erythrityl Tetranitrate, Bismuth Sub nitrite, Sodium Nitroprusside, Sodium Nitrite, Nitric Oxide, Menadione (vitamin K3), Lidocaine hydrochloride, Prilocaine hydrochloride, Amethocaine, Benzocaine, Cetacaine, Prilocaine, Procaine, Cetrimide, Bupivacaine Hydrochloride, Resorcinol, Rosanilind, Articaine, Pararosaniline Hydrochlorides, Triclocarbon Soap (TCC), Phenol, Hydroquinone, Methylene Blue, Metoclopramide Hydrochloride, Riluzole etc[33]. There have been some unusual cases of chemicals/agents causing methemoglobinemia, such as naphthalene spheres, and e-cigarettes.

Our review noticed a remarkable decrease in haemoglobin, red blood cells, haptoglobins, haematocrit, and an increase in WBC, reticulocyte count. When the reticulocyte count increases with the significant decrease in the haemoglobin, RBC, haematocrit, and haptoglobin level indicates haemolytic anaemia with the destroyed RBC in the blood circulation[34]. According to the study reported by Habib Ur Rehaman, drug-induced methemoglobinemia can result in haemolytic anaemia, especially when dapsone, sulfasalazine, or phenacetin is used. Heinz bodies (precipitated haemoglobin or globin subunits due to erythrocyte denaturation) and fragmented red blood cells are the characteristics of anaemia. Renal dysfunction may occur in the case of acute intravascular haemolysis which supports the findings of this review[35].

The basic initiation for methemoglobinemia therapy includes assessment and stabilization of the airway, breathing, and circulation are the first steps of treating metHb. It is crucial for ensuring 100% oxygen. Since dextrose is the main source of nicotinamide adenine dinucleotide in red blood cells, it should be administered. The offending agent should be withdrawn as soon as possible. Following initial stabilization, co-oximetry assists in the diagnosis. Treatment is indicated by the presence of severe symptoms or methaemoglobin levels of 25%. The administration of 1–2 mg/kg methylene blue intravenously over 5 minutes is the most commonly accepted definitive therapy for metHb. But methylene blue is contraindicated in patients with G6PD deficiency as it can reduce NADPH and can lead to haemolysis[36]. Therefore, it is usually recommended to use Ascorbic acid (Vitamin C) in G6PDD patients. Since ascorbic acid is a potent reducing agent that takes part in a variety of oxidation-reduction reactions, it has been shown to reduce methaemoglobin and treat cyanosis[37].Many drug induced adverse reactions are reported and systematic review has been conducted in recent days this adverse reactions are mainly induced by Levetiracetam[38], Valproic acid[39] and Ciprofloxacin[40] and this should be considered seriously.

There are few limitations to our review. Firstly, this review used PubMed database to find and include high-quality peer-review articles. However, this may lead to omit certain articles which are not indexed in PubMed. Secondly, this review included only English language studies that might have been contributed to the missing of some articles published in Non-English journals. Thirdly, we have included a descriptive study design which made it difficult for the quantitative synthesis. Furthermore, studies can be planned to emphasize quantitative synthesis.

Conclusion

Rasburicase can cause methemoglobinemia, which can cause mild to serious breathing complications including hypoxia, dyspnoea, and shortness of breath, which can lead to death in extreme situations. Therefore, the doctors who administer rasburicase and monitor patients should identify this severe complication early and treat it appropriately, and patients should be closely monitored. In a patient who presents with rasburicase-induced haemolysis or methemoglobinemia, it is often important to expect a diagnosis of G6PD deficiency unless otherwise confirmed and to avoid administering methylene blue, even though the patient is from a low-risk ethnicity for G6PDD.

References

1. Howard SC, Pui C-H, Ribeiro RC. Chapter 4 - Tumor Lysis Syndrome. Ren Dis cancer tients [Internet]. 2014;39–64. Available from: http://www.sciencedirect.com/science/article/pii/B9780124159488000040

2. Cairo MS, Bishop M. Tumour lysis syndrome : new therapeutic strategies and

classification. 2004;3–11.

3. Davidson MB, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Treatment of Tumor Lysis Syndrome. 2004;

4. Methemoglobinemia and Hemolytic Anemia Caused by Rasburicase Administration in a Newly Diagnosed Child With Burkitt Lymphoma / Leukemia. 2007;(January):98105.

5. Sherwood GB, Paschal RD, Adamski J. Rasburicase-induced methemoglobinemia: case report, literature review, and proposed treatment algorithm. Vol. 4, Clinical case reports. 2016. p. 315–9.

6. HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. [cited 2021 Apr 6]. Available from: www.fda.gov/medwatch

7. Poison RI, Wright RO, Hospital I, Building D. M ethemoglobinemia : Etiology , Pharmacology , and Clinical Management. 1999;(November).

8. Howick J, Chalmers I, Lind J, Glasziou P, Greenhalgh T, Heneghan C, et al. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [Internet]. [cited 2021 Mar 30]. Available from: http://www.cebm.net/index.aspx?o=5653

9. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. 2018;23(2):60–3.

10. Montgomery KW, Booth GS. A perfect storm: Tumor lysis syndrome with rasburicase-induced methemoglobinemia in a G6PD deficient adult. Vol. 32, Journal of clinical apheresis. United States; 2017. p. 62–3.

11. Ng JS, Edwards EM, Egelund TA. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. J Oncol Pharm Pract Off Publ Int

Soc Oncol Pharm Pract. 2012 Dec;18(4):425–31.

12. Bucklin MH, Groth CM. Mortality following rasburicase-induced methemoglobinemia. Ann Pharmacother. 2013 Oct;47(10):1353–8.

13. Sleutel MR, Brown W, Wells JN. Preventing Tumor Lysis Syndrome: Two Case Studies of Unexpected Outcomes. Clin J Oncol Nurs. 2016 Apr;20(2):195–200.

14. Bachmann KF, Nebiker M, Johner C, Bregy R, Schaller A, Novak U, et al. Rare Case of Transcutaneous Oxygen Desaturation in a Cancer Patient: A Case Report and Diagnostic Approach for a Recurrent Problem. A&A Pract. 2019 Feb;12(4):96–8.

15. Cheah CY, Lew TE, Seymour JF, Burbury K. Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized glucose-6-phosphate dehydrogenase deficiency. Acta Haematol. 2013;130(4):254–9.

16. Raru Y, Abouzid M, Parsons J, Zeid F. Rasburicase induced severe hemolysis and methemoglobinemia in a Caucasian patient complicated by acute renal failure and ARDS. Vol. 26, Respiratory medicine case reports. 2019. p. 142–5.

17. Oluwasanjo A, Alese O, Swierczynski S, Forman D. Rasburicase-induced methaemoglobinaemia and G6PD deficiency in an unusual suspect. Br J Haematol. 2015 Sep;170(5):595.

18. Alessa MA, Craig AK, Cunningham JM. Rasburicase-Induced Methemoglobinemia in a Patient with Aggressive Non-Hodgkin's Lymphoma. Am J Case Rep. 2015 Sep;16:590–3.

19. Roberts DA, Freed JA. Rasburicase-induced methemoglobinemia in two African-American female patients: an under-recognized and continued problem. Eur J

Haematol. 2015 Jan;94(1):83–5.

20. Ibrahim U, Saqib A, Mohammad F, Atallah JP, Odaimi M. Rasburicase-induced methemoglobinemia: The eyes do not see what the mind does not know. J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract. 2018 Jun;24(4):309–13.

21. Cooling L. Brisk clinical response to erythrocytapheresis in a G6PD-deficient patient with rasburicase-induced methemoglobinemia. Vol. 32, Journal of clinical apheresis. United States; 2017. p. 599–600.

22. Kizer N, Martinez E, Powell M. Report of two cases of rasburicase-induced methemoglobinemia. Vol. 47, Leukemia & lymphoma. United States; 2006. p. 2648–50.

23. Zhang B, Lee AI, Podoltsev N. Tumor lysis syndrome and acute anemia in an African-American man with chronic lymphocytic leukemia. Vol. 2014, Oxford medical case reports. 2014. p. 138–40.

24. Bhat P, Sisler I, Collier AB 3rd. Exchange transfusion as treatment for rasburicase induced methemoglobinemia in a glucose-6-phosphate dehydrogenase deficient patient. Vol. 51, Pediatric blood & cancer. United States; 2008. p. 568.

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

26. Reeves DJ, Saum LM, Birhiray R. I.V. ascorbic acid for treatment of apparent rasburicase-induced methemoglobinemia in a patient with acute kidney injury and assumed glucose-6-phosphate dehydrogenase deficiency. Am J Heal Pharm AJHP Off J Am Soc Heal Pharm. 2016 May;73(9):e238-42.

27. Jung S, Sayad K, Staitieh BS. Low Hemoglobin Saturation in the Setting of Hyperuricemia. Ann Am Thorac Soc. 2019 Nov;16(11):1447–50.

28. Sonbol MB, Yadav H, Vaidya R, Rana V, Witzig TE. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. Am J Hematol. 2013 Feb;88(2):152–4.

29. Bauters T, Mondelaers V, Robays H, De Wilde H, Benoit Y, De Moerloose B. Methemoglobinemia and hemolytic anemia after rasburicase administration in a child with leukemia. Int J Clin Pharm. 2011 Feb;33(1):58–60.

30. Borinstein SC, Xu M, Hawkins DS. Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. Vol. 50, Pediatric blood & cancer. United States; 2008. p. 189.

31. Mosby's Diagnostic and Laboratory Test Reference - 14th Edition [Internet]. [cited 2021 Mar 19]. Available from: https://www.elsevier.com/books/mosbys-diagnostic-and-laboratory-test-reference/pagana/978-0-323-60969-2

32. Tumor Lysis Syndrome: EBM guidelines.

33. Alanazi MQ. Drugs may be Induced Methemoglobinemia. J Hematol Thromboembolic Dis. 2017;06(01):5–9.

34. Haptoglobin | Lab Tests Online [Internet]. [cited 2021 Mar 20]. Available from: https://labtestsonline.org/tests/haptoglobin

35. Rehman HU. Methemoglobinemia. West J Med [Internet]. 2001 [cited 2021 Mar 20];175(3):193–6. Available from: /pmc/articles/PMC1071541/

36. Rino PB, Scolnik D, Fustiñana A, Mitelpunkt A, Glatstein M. Ascorbic acid for the

treatment of methemoglobinemia: The experience of a large tertiary care pediatric hospital. Am J Ther. 2014;21(4):240–3.

37. Abdelkader SI, Mohmoud AE. Effective role of ascorbic acid as an alternative treatment of methemoglobinemia: A case report. Int J Case Reports Images. 2018;9(June):1.

38. Rashid M, Rajan AK, Chhabra M, Kashyap A. Levetiracetam and cutaneous adverse reactions: A systematic review of descriptive studies. Vol. 75, Seizure. W.B. Saunders Ltd; 2020. p. 101–9.

39. Rashid M, Kashyap A, Undela K. Valproic acid and Stevens-Johnson syndrome: a systematic review of descriptive studies [Internet]. Vol. 58, International Journal of Dermatology. Blackwell Publishing Ltd; 2019 [cited 2021 Apr 18]. p. 1014–22. Available from: https://pubmed.ncbi.nlm.nih.gov/30809807/

40. Kashyap A, Sreenivasan S, Rajan AK, Rashid M, Chhabra M. Ciprofloxacin-induced cutaneous adverse drug events: a systematic review of descriptive studies. J Basic Clin Physiol Pharmacol [Internet]. 2021 Mar 16 [cited 2021 Apr 18];0(0). Available from: https://pubmed.ncbi.nlm.nih.gov/33725760