A Retrospective Review of Mercaptopurine Metabolism Reveals High Rate of Patients with Suboptimal Metabolites Successfully Corrected with Allopurinol

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Abstract

Background: 6-Mercaptopurine (6-MP) is the most frequently used chemotherapy agent in the management of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). Skewed drug metabolism can decrease the effectiveness of 6-MP and result in unnecessary toxicities. Current guidelines suggest holding or lowering 6-MP doses with toxicity; however, this approach results in decreased intensity of 6-MP treatment, potentially risking disease relapse. Allopurinol can alter 6-MP metabolism to maximize therapeutic effects while reducing adverse toxicities. Methods: This single institution, retrospective cohort study, quantified the incidence of mercaptopurine related toxicities and the number of mercaptopurine metabolite shunters. For those patients started on allopurinol, we collected clinical follow up information. Results: Of 42 eligible patients, 74% and 88% had at least one episode of hypoglycemia and elevated alanine aminotransferase (ALT), respectively. Mercaptopurine metabolite data were available in 66% of our patients. 6-methylmercaptopurine nucleotide (6-MMPN) levels were >10 000 in 55% of the cohort, suggesting 6-MP shunting. Allopurinol was initiated for metabolite and laboratory derangements in 12 of 23 shunters. All patients who received allopurinol had resolution of toxicities. Discussion: In our population of children and young adults treated for ALL and LL, we found a high incidence of shunters, many with associated toxicities. The patients who received allopurinol in combination with scheduled chemotherapy showed reversal of undesired toxicities, suggesting combination therapy may be beneficial for certain patients. Based on our institutional experience, we propose an algorithm to incorporate allopurinol into chemotherapy regimens for patients with ALL or LL who have inappropriate 6-MP metabolism.

Introduction

Advances in multi-agent chemotherapy for treatment of acute lymphoblastic leukemia (ALL) have improved overall survival to nearly 90% [1]. Purine antimetabolites play a crucial role in these excellent survival rates. 6-Mercaptopurine (6-MP) currently forms the backbone of all lymphoblastic leukemia maintenance treatment protocols and 6-MP dose intensity has proven to be one of the most important determinants of overall event free survival[2,3]. Although typically well tolerated, some individuals experience undesirable side effects including hypoglycemia, hepatotoxicity, and pancreatitis. A report from Children's Hospital Los Angeles of a single institution cohort indicated 27% of patients experienced hepatotoxicity and 11% developed pancreatitis. Of these, 38% of patients with hepatotoxicity and 67.9% of those with pancreatitis had treatment modifications to include dose reduction or chemotherapy delays [4].

6-MP is metabolized in 3 distinct pathways leading to the production of thiouric acid, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine nucleotides (6-MMPN). Around 70% of the drug is metabolized via xanthine oxidase (XO) through the intermediate thioxanthine (TX) to the inactive metabolite thiouric acid (6-TU) and excreted in urine [5]. The second pathway is via enzymes of the purine salvage

pathway such as hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and inosine-5'-monophosphate dehydrogenase (IMPDH) to form the thioguanine nucleotide (6-TGN) that is believed to mediate the main therapeutic effects of 6-MP (Figure 1). 6-TGN is a purine agonist that incorporates into DNA of leukocytes inhibiting DNA synthesis and downstream T-cell proliferation leading to the ultimate immunosuppressive effect of the chemotherapy[5,6]. 6-TGN is toxic to all cells and in excess poses an increased risk for severe myelosuppression [6,7]. The final arm is methylation of 6-MP by thiopurine-S-methyltransferase (TPMT) to form 6-methylmercaptopurine (6-MMP), an inactive molecule that has no known biologic effect but can be further metabolized by HGPRT to form 6-methylmercaptopurine nucleotide (6-MMPN), which also inhibits*de novo* purine synthesis [5,6]. 6-MMPN is felt to be the source of the adverse effects of 6-MP therapy, as hypoglycemic episodes during fasting have been associated with high levels of 6-MMPN[8] and hepatotoxicity has been associated with 6-MMPN levels >5 000 ρmol/8x10^8 erythrocytes.[9,10].

Allopurinol is a xanthine oxidase inhibitor which results in increased metabolism of 6-MP toward 6-TGN but also away from 6-MMPN[11-13]. How allopurinol results in decreased 6-MMPN is not well understood as it is not known to inhibit the TPMT enzyme. Nevertheless, numerous prior case studies have demonstrated clinical effectiveness for ameliorating 6-MP-induced hypoglycemia, hepatotoxicity, and recurrent pancreatitis by dose reduction of 6-MP combined with allopurinol when 6-TGN levels are increased with decreased levels of 6-MMPN [14-17].

The goal of this study is to characterize the incidence of symptomatic hypoglycemia, hepatotoxicity, and pancreatitis as well as the incidence of 6-MP metabolite shunting (overproduction of 6-MMPN with underproduction of 6-TGN) within a single institution practice. We will then describe cases where allopurinol was used and its effects on symptoms and metabolite levels. We further propose an algorithm to combine allopurinol with 6-MP to allow therapeutic efficacy while minimizing toxicity.

Materials and Methods

We performed a single institution, IRB approved, retrospective study to quantify and characterize the rate of "shunters" treated in our center. Expert chart review by the authors was conducted on each eligible patient. Patients were included in our cohort if they were aged 0-30 years and treated for B cell or T cell ALL or lymphoblastic lymphoma (LL) at our institution over a 10-year period from January 1, 2009 to June 1, 2019. Additional inclusion criteria included receiving maintenance therapy at our institution for at least a 12-month period. All of those treated for less than 12 months were excluded from data collection and analysis. Clinical demographics including age, gender, ethnicity, disease type, risk stratification, and treatment protocol were collected. Incidents of hypoglycemia (glucose <74 mg/dL), hepatic inflammation (Alanine aminotransferase [ALT] >123 U/L), pancreatitis (amylase >100 U/L or lipase >60 U/L), and hypogammaglobulinemia (IgG <400 mg/dL) were recorded. We queried the treatment records for the maximum dose of 6-MP prescribed during maintenance therapy, identifying if an individual had their 6-MP dosing increased above 100%. If available, thiopurine metabolite levels were recorded, noting levels of 6-MMPN greater than 10 000 pmol/8 x 10^8 RBC. We defined "shunters" as individuals who had 6-MMPN levels greater than 10 000 pmol/8 x 10^8 RBC. If a patient was started on allopurinol, we noted the dose(s) of allopurinol at the start of therapy and throughout the treatment course, the effects of the allopurinol intervention on the aforementioned lab values, and the patient's clinical course. Descriptive statistics were calculated in Stata ver. 16.

Results

Forty-two patients were eligible for inclusion in our chart review. All patients in this cohort had wild type TPMT genotypes. The demographic information of this cohort can be found in Table 1. Of these, 30 patients (71.4%) were under the age of 10. There was a predominance of males, 28 (66.6%) and Caucasians, 29 (69%). The diagnoses treated included B cell ALL (78.6%), T cell ALL (14.3%), and LL (7.1%). We documented when the following laboratory values were out of the identified normal ranges at any time during maintenance chemotherapy treatment (and the number of occurrences): ALT, glucose, immunoglobulin G, amylase, lipase, and the 6-MP metabolites 6-MMPN and 6-TGN. Table 2 displays the toxicities experienced in our cohort. Seventy four percent of patients had a least one episode of documented hypoglycemia and 88%

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had at least one episode of elevated ALT >3 times the upper limit of normal. Shunting of 6-MP to the toxic metabolite 6-MMPN was observed in 54% of the patients (Table 3). Allopurinol was used in 12 patients; most had improvement in clinical course and metabolite profiles (Figure 2, Table 3). For those who were treated with allopurinol, the ratio of 6-MMPN/6-TGN changed from a mean of 92 (standard deviation 16.8) to a mean of 8.6 standard deviation 12.9). Forty five percent (17/38) of all males reviewed were shunters, while only 25% (6/24) of females experienced shunting (Table 1). When evaluated by age, 41% (18/44) patients [?] 10 years were shunters, while only 27% (5/18) of those > 10 years experiencing shunting (Table 1).

The series of 12 patients who received allopurinol demonstrated safety and efficacy. These patients experienced no direct side effects from the allopurinol, nor did they experience any increased toxicity of chemotherapy as a result of the allopurinol. All patients treated with allopurinol remain alive and in remission as of 1 Jun 2019, the longest being 6 years post-treatment. Transaminitis resolved for all twelve patients. Three patients with symptomatic hypoglycemia related to mercaptopurine therapy had improvement not only in symptoms but also in measured glucose levels during clinic encounters. All three patients with acute pancreatitis during maintenance had experienced acute pancreatic episodes prior to the start of maintenance therapy. Two of these went on to develop chronic pancreatitis that flared during maintenance.

Discussion

In our small cohort, we found a much higher incidence of individuals with documented 6-MMPN levels above 10 000 pmol/8 x 10^8 RBC than expected based on previous reports[18,19]; over 50% of our patients had shunting of 6-MP with associated toxicities. By contrast, previously documented rates of symptomatic 6-MMPN derangements in individuals were 20-30% in gastroenterology literature [19,20]. It should be noted that the 6-MP dosing used in inflammatory bowel disease treatment is lower than that used in oncology. This higher dosing may explain the increased incidence of shunting in our oncology population. Our experience suggests that 6-MP metabolite levels should be monitored during maintenance therapy, particularly in the setting of known 6-MP toxicities, to prevent chemotherapy holds and dose reductions. In addition, because it is standard protocol to escalate 6-MP dosing when a patient's absolute neutrophil count (ANC) is not adequately suppressed, we have noted that increases in 6-MP doses further exacerbate shunting and its adverse effects.

Allopurinol has a well-documented safety profile in its use for gout[21]. A similar safety profile was documented in our cohort. There were no direct adverse events after initiation of allopurinol in our patients despite the risk for increased myelosuppression if dosing is not carefully determined. Previously, because 6-MP was only available in 50 mg tablets, it was difficult to make fine dose adjustments in order to better establish the therapeutic dose. Combined therapy with allopurinol amplifies the clinical effect of 6-MP dose changes and it can cause undesired myelosuppression if dosing is not carefully titrated. We, therefore, provide an algorithm for combination therapy with a simple protocol for determining correct dosing for patients that has worked well for our center (Figure 3). In addition, the FDA approval of a liquid formulation of mercaptopurine makes it easier to manage combination therapy. In those patients in our series who were treated with allopurinol there was no apparent decrement in event free or survival outcomes.

Our series demonstrates efficacy for the use of allopurinol in the management of mercaptopurine side effects. Adverse effects related to mercaptopurine therapy including hepatotoxicity, hypoglycemia, and acute pancreatitis were reversed in all patients. While the chronic pancreatitis with insulin-dependent diabetes experienced by one patient was unchanged by the addition of allopurinol to the treatment regimen, this likely reflects the damage from the initial insult to the pancreas and not a lack of improvement with allopurinol. Patients started on combination therapy with allopurinol experienced reversal of undesired toxicities, suggesting that combination therapy may be beneficial for many more patients in the future.

Interestingly, a much higher percentage of males than females experienced shunting in our cohort. One possible explanation for this difference is the higher levels of TPMT activity often found in males[22] that could theoretically result in higher levels of 6-MMPN levels if this higher activity were not balanced by the

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other enzymatic pathways. TPMT activity has also been shown to have racial differences, with Caucasians having higher TPMT levels, which would suggest a higher rate of shunting among Caucasian patients[23]. Perhaps due to our small cohort size we did not find significant differences between ethnicities, although it is interesting to note that 4 of the 5 African American patients in our cohort were 'shunters. Of course, larger studies may be able to examine this finding in more detail and are warranted.

It has become our institution's practice to monitor for signs of aberrant mercaptopurine metabolism, including hepatotoxicity, neutropenia (or neutrophilia), hypoglycemia, and pancreatitis. In these settings we begin monitoring 6-MMPN and 6-TGN levels. For those with markedly elevated 6-MMPN >10 000 pmol/8 x 10^8 RBC, we consider the addition of allopurinol. Considerations for the addition of allopurinol in each case include severity of toxicity and symptoms as well as compliance with current chemotherapy regimens. For those patients who agree to treatment with the combination of allopurinol-mercaptopurine we start with an age-based oral allopurinol dose (50 mg daily for age <5 years, 100 mg daily for age 5-10 years, 200 mg daily for age 10-15 years, and 300 mg daily for those over 15 years). Because of the enzyme blockade by allopurinol, we concomitantly reduce 6-MP to 25mg/m^2/dose. For our younger children, utilizing liquid mercaptopurine can be beneficial in order to have tighter titration of the dose and effect. We then adjust 6-MP and allopurinol doses to achieve a goal of normalization of toxicities, absolute neutrophil count in the therapeutic window of 500-1 500 cells/μL and a 6-MMPN level of <5 000 pmol/8 x 10^8 RBC. If the 6-MMPN level is not substantially decreased with the addition of allopurinol, a higher dose of allopurinol dose should be attempted as there are individual variations in allopurinol effectiveness that require some patients to be on a higher allopurinol dose. Steroid and vincristine dosing during maintenance were not adjusted. Methotrexate dosing was also not adjusted during early phases of allopurinol-mercaptopurine titration, however if after several months ANC levels persisted >1500 cells/μL, then increasing methotrexate to 125% dosing was considered. Figure 3 offers an algorithmic approach to management.

It should be noted that the mechanism by which the addition of allopurinol to mercaptopurine therapy results in increased 6-TGN and decreased 6-MMPN is not fully understood. Preliminary laboratory experiments performed at our institution showed that allopurinol may cause decreased 6-MMPN levels due to tissue specific effects of 6-MP metabolism[24]. When 6-TGN and 6-MMPN levels are measured clinically, the levels are determined from red blood cells which are not undergoing cell division. In previous treatment protocols incorporating 6-Thioguanine (6-TG), which is directly converted to 6-TGN without any other metabolism, the 6-TG was found to be more hepatotoxic than 6-MP. Patients who are clinically treated with combination therapy have much higher 6-TGN levels than patients who are only on 6-MP and thus previous guidelines for 6-TGN therapeutic levels cannot be used to determine dosage efficacy. In addition, the extremely high 6-TGN levels, we achieved, with combination therapy while known to cause myelosuppression, did not result in hepatotoxicity. Based on our preliminary data, we suggest these changes in metabolite levels are due to the tissue specific effects of allopurinol on 6-MP metabolism; but further studies are required to confirm this finding.

One major limitation in this analysis is missing data for some individuals. Metabolite data was not checked in all of those who were eligible. Additionally, the frequency of checking metabolite data in patients also differs among those who were started on allopurinol. Of those who were started on allopurinol, Patients 2 and 12 were started based on clinical toxicities and did not have metabolite levels checked prior to allopurinol start. It is important to note that this lack of metabolite data could potentially indicate that our findings are an underestimation of the incidence of mercaptopurine metabolite shunting. Additionally, 6-MMPN and 6-TGN levels for our patients who did not exhibit clinical toxicities were not obtained for most of the cohort; these levels could have been useful to better establish a normal profile of 6-MMPN and 6-TGN levels, as well as a therapeutic window for the ratio of 6-MMPN:6-TGN which could be useful for guiding the initiation and benefits of allopurinol to mercaptopurine therapy. With use of this proposed algorithm, we think combination therapy has the potential to become routine practice in oncology.

Conclusions

1. The incidence of aberrant metabolism of mercaptopurine in our study was above 50% and is likely

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more prevalent in the ALL and LL populations than previously reported
2. Utilizing our proposed algorithm for introduction the of allopurinol to mitigate mercaptopurine metabolite toxicity is both a safe and effective intervention, but does require close interval monitoring
3. Identification of a therapeutic 6-MMPN:6-TGN ratio may be helpful in guiding decisions to start hybrid allopurinol-mercaptopurine therapy as well as guide dose titration.

Conflicts of Interest

No conflicts of interest to disclose.

Disclaimer

The views expressed in the publications are those of the authors and do not reflect the official position of the Army, Navy, Air Force, Department of Defense, or the U.S. Government.

Off Label Drug Phrase

Allopurinol inhibits the enzyme xanthine oxidase and is commonly used for prevention of tumor lysis syndrome and gout. However, it is understood that allopurinol also effects the metabolism of 6-mercaptorpurine (6-MP). Allopurinol directs 6-MP metabolism toward 6-thioguanine (6-TGN), the desired product, and away from 6- methylmercaptopurine (6-MMPN). 6-MMPN is associated with increased toxicity in patients. We describe the successful incorporation of allopurinol therapy in many of our patients with abnormal 6-MP metabolism.

Data Statement : The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Pui CH, Yang JJ, Hunger SP, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *J Clin Oncol.*2015;33(27):2938-2948.

2. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. *J Clin Oncol.* 2012;30(17):2094-2101.

3. Relling MV, Hancock ML, Boyett JM, Pui CH, Evans WE. Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. *Blood.* 1999;93(9):2817-2823.

4. Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens.*Pediatr Blood Cancer.* 2018;65(3).

5. Weinshilboum R. Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. *Drug Metab Dispos.*2001;29(4 Pt 2):601-605.

6. Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol.* 1992;43(4):329-339.

7. Bostrom B, Erdmann G. Cellular pharmacology of 6-mercaptopurine in acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol.*1993;15(1):80-86.

8. Maelachuri S, Gandrud L, Bostrom B. The association between fasting hypoglycemia and methylated mercaptopurine metabolites in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.*2014;61(6):1003-1006.

9. Adam de Beaumais T, Fakhoury M, Medard Y, et al. Determinants of mercaptopurine toxicity in paediatric acute lymphoblastic leukemia maintenance therapy. *Br J Clin Pharmacol.* 2011;71(4):575-584.

10. Nygaard U, Toft N, Schmiegelow K. Methylated metabolites of 6-mercaptopurine are associated with hepatotoxicity. *Clin Pharmacol Ther.* 2004;75(4):274-281.

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11. Blaker PA, Arenas-Hernandez M, Smith MA, et al. Mechanism of allopurinol induced TPMT inhibition. *Biochem Pharmacol.*2013;86(4):539-547.

12. Roberts RL, Gearry RB, Barclay ML. Allopurinol-thiopurine combination therapy in inflammatory bowel disease: are there genetic clues to this puzzle? *Pharmacogenomics.* 2010;11(11):1505-1508.

13. Zimm S, Collins JM, O'Neill D, Chabner BA, Poplack DG. Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther.*1983;34(6):810-817.

14. Brackett J, Schafer ES, Leung DH, Bernhardt MB. Use of allopurinol in children with acute lymphoblastic leukemia to reduce skewed thiopurine metabolism. *Pediatr Blood Cancer.*2014;61(6):1114-1117.

15. Giamanco NM, Cunningham BS, Klein LS, Parekh DS, Warwick AB, Lieuw K. Allopurinol Use During Maintenance Therapy for Acute Lymphoblastic Leukemia Avoids Mercaptopurine-related Hepatotoxicity. *J Pediatr Hematol Oncol.* 2016;38(2):147-151.

16. Zerra P, Bergsagel J, Keller FG, Lew G, Pauly M. Maintenance Treatment With Low-Dose Mercaptopurine in Combination With Allopurinol in Children With Acute Lymphoblastic Leukemia and Mercaptopurine-Induced Pancreatitis. *Pediatr Blood Cancer.* 2016;63(4):712-715.

17. Zhang M, Bostrom B. Allopurinol reverses mercaptopurine-induced hypoglycemia in patients with acute lymphoblastic leukemia.*F1000Res.* 2019;8:176.

18. Rahhal RM, Bishop WP. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2008;14(12):1678-1682.

19. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology.* 2000;118(4):705-713.

20. Dubinsky MC, Yang H, Hassard PV, et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. *Gastroenterology.*2002;122(4):904-915.

21. Castrejon I, Toledano E, Rosario MP, Loza E, Pérez-Ruiz F, Carmona L. Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis.*Rheumatology international.* 2015;35(7):1127-1137.

22. Asadov C, Aliyeva G, Mustafayeva K. Thiopurine S-Methyltransferase as a Pharmacogenetic Biomarker: Significance of Testing and Review of Major Methods. *Cardiovasc Hematol Agents Med Chem.*2017;15(1):23-30.

23. Cooper SC, Ford LT, Berg JD, Lewis MJ. Ethnic variation of thiopurine S-methyltransferase activity: a large, prospective population study. *Pharmacogenomics.* 2008;9(3):303-309.

24. Cunningham B, Krishnamurthy J, Deutsch J, Flora MN, Lieuw K. 360 Elucidating the Mechanism of 6-Mercaptopurine Induced Hepatotoxicity and How Combination with Allopurinol Eliminates the Hepatotoxicity.*Gastroenterology.* 2016;150(4):S1030.

Figure Legends

FIGURE 1 Proposed mechanism of effect of allopurinol on 6-MP metabolism

FIGURE 2 Changes in 6-mercaptopurine metabolites before and after allopurinol

FIGURE 3 Algorithm for allopurinol incorporation with 6-MP metabolite derangements and/or toxicity

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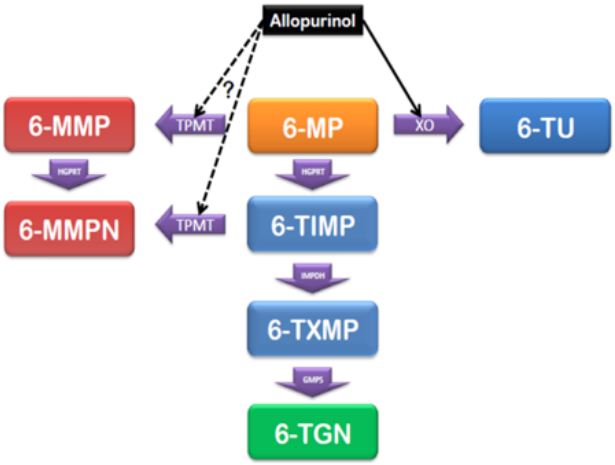
FIGURE 1 Proposed mechanism of effect of allopurinol on 6-MP metabolism



6-MMP – 6-methylmercaptopurine; 6-MMPN – 6-meythmercaptopurine nucleotide; TMPT - thiopurine-S-methyltransferase; 6-TGN – 6-thoiguanine nucleotide; 6-TU – 6-thiouric acid; 6-TIMP – 6-thiosine; 5'-monophosphage; 6-TXMP – 6-thioxanyhylic acid

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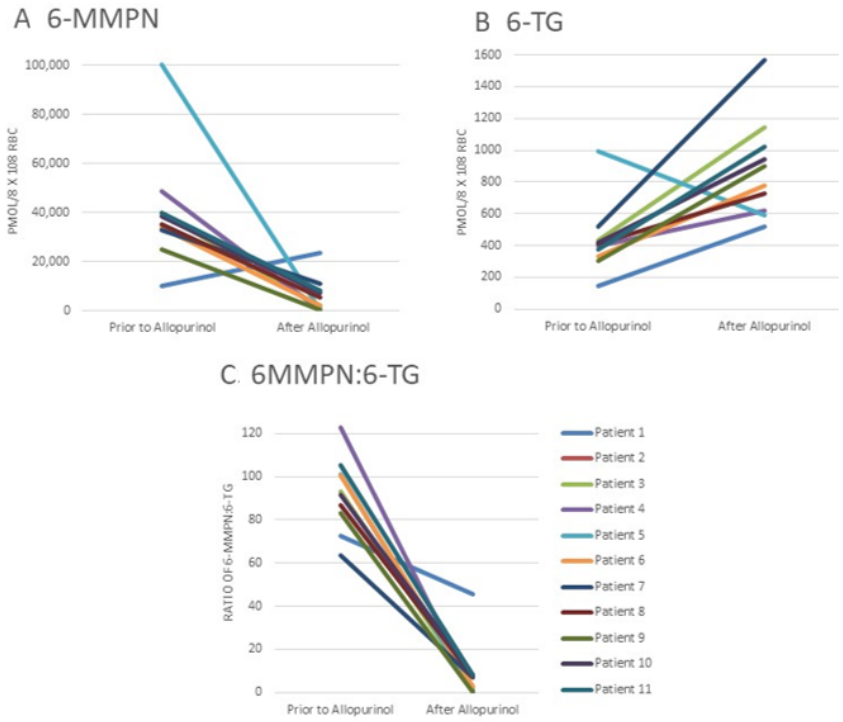
FIGURE 2 Changes in 6-mercaptopurine metabolites before and after allopurinol



Data points represent the maximum level for each metabolite and ratio before and after allopurinol for: 6-MMPN (A) 6-TG (B) and 6-MMPN:6-TG ratio (C).
Patient 2 and 12 did not have available metabolite levels prior to allopurinol start.
6-MMPN – 6-methylmercaptopurine nucleotide; 6-TG – 6-thioguanine

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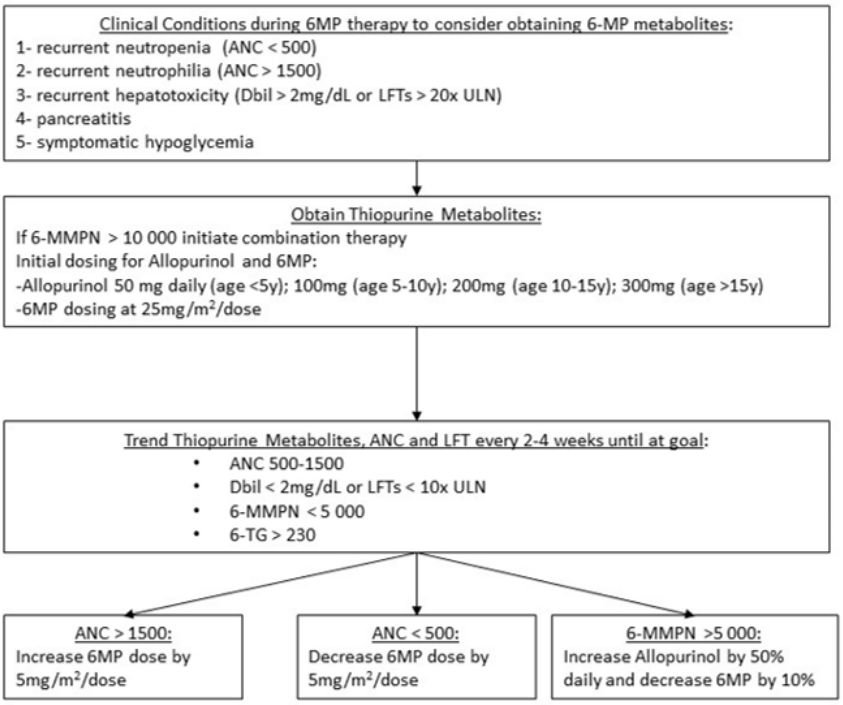
FIGURE 3 Algorithm for allopurinol incorporation with 6-MP metabolite derangements and/or toxicity



6MP – 6-mercaptopurine; dBili – direct bili; LFT – liver function test; ULN – upper limit of normal; 6-MMPN – 6 methylmercaptopurine nucleotide; ANC – absolute neutrophil count; 6-TG – 6-thioguanine

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