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Efficacy and safety of azathioprine in patients with Cronkhite-Canada syndrome: a case series from Peking Union Medical College Hospital

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Abstract

Background Cronkhite-Canada syndrome (CCS) is a rare non-hereditary chronic inflammatory disease characteristic of gastrointestinal polyps and ectodermal abnormalities. Corticosteroid therapy is the mainstay medication for CCS. Few studies indicated immunosuppressants might be the choices for patients with steroid refractory, steroid dependent or intolerant.

Aim To examine the efficacy and safety of azathioprine (AZA) in CCS patients.

Method We retrospectively reviewed the records of 12 CCS patients treated with azathioprine between July 2014 and October 2023 and the clinical data including demographic characteristics, treatment regimen and adverse events were subsequently collected and analyzed. The genetic variants of *TPMT* and *NUDT15* genes were also retrospectively assessed using sanger sequencing in 11 patients.

Outcome All patients were in active stage at baseline and 9 patients (75%) were in combination with corticosteroid. On account of the indication, 6 patients were steroid dependent or intolerant and another 6 patients needed augmentation therapy. The target dose of AZA was 1.0 to 1.5 mg/kg per day. Ten (83.3%) patients achieved clinical response, of whom 3 cases had endoscopic remission and 5 cases had endoscopic improvement respectively. Three (25%) patients suffered from pneumocystis carinii pneumonia, liver dysfunction and leukopenia, respectively, resulting in cessation of AZA in the initial 3 months. Four heterozygous missense variants of *TPMT* and *NUDT15* were identified in four patients. One patient who had *TPMT**6 and took AZA with the dose of 2.04 mg/kg per day suffered from severe leukopenia.

Conclusion Azathioprine might be a good alternative medication in CCS patients who are steroid dependent or intolerant, or need augmentation therapy. The adverse events should be closely monitored especially myelosuppression and the tests of *TPMT* and *NUDT15* genotypes before therapy may be helpful for medication guidance.

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Keywords Cronkhite-Canada syndrome, Azathioprine, Efficacy, Safety

Introduction

Cronkhite-Canada syndrome (CCS) is a rare and non-inherited syndrome, which is characteristic of gastrointestinal hamartomatous polyps and ectodermal manifestations including alopecia, skin hyperpigmentation and nail dystrophy. The typical gastrointestinal (GI) symptoms include diarrhea, abdominal pain and anorexia, as well as numerous sessile polyps with abnormal inter-polyp mucosa throughout whole GI tract sparing of esophagus is typical of endoscopic findings [1]. The diagnosis of CCS is established on the combination of clinical characteristics, pathological findings and radiologic manifestations, with exception of other hereditary polyposis diseases. The 5-year mortality rate for CCS has been previously reported to be 55%, and its poor prognosis can be partly explained by fatal complications linked to malnutrition, such as embolism, sepsis and heart failure [2]. Recently our previous study showed the updated 5-year overall survival rate was up to 87.4% [3] and it was in part attributed to comprehensive therapeutic regimens including immunosuppressive therapy (mainly corticosteroids), nutritional support and prompt surgical procedures. Although its causes and pathogenesis are not well understood, CCS is generally thought to involve a immune-related mechanism [4], and such studies have confirmed the efficacy of corticosteroids as first-line therapy in induction and relapse prevention, with long-term response rate at 60–70% [3–5]. However, approximately a third of patients suffered relapse of diseases as steroids tapered, and steroid-sparing strategies studied by small-size cohorts and case reports revealed that immunosuppressants such as azathioprine (AZA), and cyclosporine A (CsA) may be alternative choices [3–7]. The role of AZA in the medications of CCS patients still needs to be unravelled. Recently, *Thiopurine methyltransferase* (*TPMT*) and *nudix hydrolase 15 (NUDT15)* genotype surveillance was recommended before medication therapy to guide drug optimization because the reduced activity of TPMT and NUDT15 led to the accumulation of toxic metabolites with increased risks of myelotoxicity in azathioprine administration, resulting in discontinuation of therapy [8]. Therefore, this study aimed to retrospectively explore the efficacy and safety of azathioprine on CCS patients and test the potency of genotype surveillance for drug optimization.

Method

Patient selection

The PUMCH-CCS cohort database was reviewed and patients who received azathioprine therapies during July 2014 and October 2023 were enrolled. The inclusion criteria involved: 1) the diagnosis of CCS was confirmed by two experienced gastrointestinal physicians (Ji LI and Jingnan LI) based on the previous diagnostic criteria [3]; 2) all patients were followed up for more than 3 months after AZA medication; 3) all patients gave signed informed consents. The exclusion criteria involved: (1) patients who failed to take AZA following the prescription of physicians; (2) patients lost to follow-up within 3 months after therapy as AZA is a slow-acting drug estimated to require at least 3 months to take effect.

The baseline clinical features were collected before the initiation of AZA therapy. The clinical manifestations, laboratory tests and endoscopic findings were subsequently recorded. The indications for AZA therapy are listed as follows: (1) patients required augmentation treatment combined with corticosteroids; (2) patients showed dependent on or refractory to adequate corticosteroids (dose equal to prednisone 0.75-1 mg/kg per day). The doses of azathioprine started at 50 mg per day and thereafter, the target dose of 1.0 to 1.5 mg/kg per day were attained during the period of two to three months.

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (I-22PJ1077), and informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Follow-up

Follow-ups by phone calls or face-to-face interviews were made and the endpoint of follow-up was the withdrawal of azathioprine for any reason. The definition of clinical and endoscopic response was in consistence with that previously reported [3]. The clinical remission was defined as the disappearance of GI symptoms and ectodermal abnormalities. The clinical response was defined as the improvement of clinical symptoms more than 50% compared with baseline. The endoscopic remission was defined as having no more than five polyps left in the GI tract and normal adjacent mucosa. The endoscopic response was defined as more than 50% involved GI tract with the regression of polyps and mucosal inflammation.

Genotyping analysis

The genotypes of *TPMT* and *NUDT15* were retrospectively tested using Sanger sequencing in 11 patients of this cohort. NUDT15*3, TPMT*2, *3A, *3B, *3 C and *6 were recommended for azathioprine dose tailoring with a level of evidence 1 A [9], which were systemically analyzed. The allele functionality was assessed according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline [10].

Statistical analysis

Continuous variables were expressed as the mean and standard deviation for those fitting a normal distribution, as well as Medians and quartiles [M (P25, P75)] for those not fitting a normal distribution. We used Microsoft Excel 2022 software to perform descriptive statistics.

Result

Baseline characterization

Ten patients (83.3%) were male, and the median age (P25, P75) at diagnosis was 55.5 (21, 66) years old. The median interval from the onset of symptoms to the diagnosis was 4 (1, 42) months. In addition to variable degrees of diarrhea presented by all patients, extraintestinal manifestations such as alopecia and hypogeusia were included. Comorbidities were also shown in Table 1. All cases were in active phase before initiation of azathioprine treatment, 75% (9/12) of whom were in combination with corticosteroids.

Table 1 Baseline Characteristics of CCS patients taking azathioprine

Number	Gender	Age at diagnosis	Duration of Disease (years)	Comorbidities
1	M	58	9	Interstitial lung disease, allergic asthma, dry eye syndrome
2	M	55	8	Rectal prolapse
3	M	64	7	Right orbital mucosa associated lymphoid tissue lymphoma
4	F	52	7	Gastroesophageal reflux disease, Hashimoto's thyroiditis
5	M	57	7	Hypertension
6	M	65	4	Vitiligo, IgG4 associated disease, hypoalbuminemia
7	M	21	2	Chronic hepatitis B carrier
8	M	52	1	hypoalbuminemia
9	M	60	1	Hypertension, latent TB infection, emphysema
10	M	49	5	No
11	F	66	13	Hypertension, diabetes, severe osteoporosis, hyperlipidemia
12	M	58	3	No

TB, tuberculosis

The efficacy of AZA medication

The indications of azathioprine included intensive therapy in 6 patients, and dependence or intolerance of steroids in the remaining 6 patients. The median follow-up period was 16 (1, 99) months. No deaths were recorded. The clinical remission and response were respectively observed in 80.0% (8/10) and 20.0% (2/10) of cases (Supplementary Fig. 1). Among the endoscopic evaluations of eight cases, three (37.5%) of patients achieved endoscopic remission, and the other five (62.5%) responded with endoscopic improvements, as shown in Table 2 and Supplementary Figs. 2 and 3. Among all, two cases with azathioprine monotherapy treatment achieved remission both clinically and endoscopically.

The adverse effects of AZA medication

During the follow-up, 41.7% (5/12) of patients suffered from adverse events, including 2 patients with leukopenia, 1 patient with *Pneumocystis carinii* pneumonia (PCP) infection, 1 patient with varicella zoster virus infection, and 1 patient with liver dysfunction. Finally, 25% (3/12) of patients discontinued their medications within 2 to 3 months after starting azathioprine on account of adverse events (PCP infection, liver dysfunction and severe leukopenia, respectively), whereas the other patients (9/12) showed good tolerance to the targeted doses (1.0 to 1.5 mg/kg per day) of azathioprine and maintained clinical remission. With regard to adverse effect, Case 8 suffered PCP infection with combination of AZA and full-dose corticosteroids therapy, and thereafter discontinued AZA therapy. The case 8 finally recovered with anti-PCP therapy using trimethoprim sulfamethoxazole and achieved remission with low-dose maintenance steroids. The case 9 presented liver dysfunction with administration of azathioprine, resulting in drug cessation and turned to methotrexate therapy to maintain remission. The case 11 who received 2 mg/kg per day of azathioprine suffered from severe AZA-induced leukopenia and subsequent genotyping analysis showed the detection of one uncertain function allele (*TPMT**6), which may explain the genetic predisposition to the drug-related myelosuppression. The case 11 discontinued azathioprine therapy and the white blood cell counts were monitored to gradually return to normal.

Genotypes of *TPMT* and *NUDT15*

After sanger sequencing on *NUDT15**3, *TPMT**2, *3A, *3B, *3 C and *6 among 11 patients, four heterozygous missense variants of *TPMT* and *NUDT15* were identified in four patients respectively (Table 3). *NUDT15*3* was detected in three patients (patient 3, patient 10, patient 12), and only one patient suffered from transient mild leukopenia (patient 3). According to CPIC guidelines, these patients are NUDT15 intermediate metabolizer.

Table 2 Treatment regimens and adverse events of CCS patients

No.	Indication for AZA	Dose of AZA at onset (mg/kg per day)	Duration of AZA (months)	Duration of steroids (months)	Combined medications	Clinical Effectiveness	Endoscopic Effectiveness	Adverse events
1	Augmentation	0.91	98	98	Pred 10 mg qd	Remission	Remission	No
2	Steroid-dependent	1.33	24	5	Pred 40 mg qd, tapering	Remission	Response	No
3	Steroid-intolerant	0.81	53	53	Pred 5 mg qd, 5-ASA 1 g tid	Remission	Response	Leukopenia
4	Augmentation	1.59	60	NA	NA	Remission	Remission	No
5	Steroid-intolerant	1.52	52	NA	NA	Remission	Response	No
6	Augmentation	1.03	17	17	Pred 40 mg qd, tapering	Remission	Response	VZV infection
7	Augmentation	1.70	14	14	Pred 20 mg qd, tapering	Response	Recurrence	No
8	Augmentation	1.00	1	1	MP 40 mg qd, tapering	NA	NA	PCP infection
9	Steroid-dependent	1.00	2	2	Pred 55 mg qd, tapering	NA	NA	Liver dysfunction
10	Augmentation	0.67	4	4	Pred 10 mg qd	Remission	Response	No
11	Steroid-intolerant	2.04	3	NA	Tripterygium glycoside	Response	NA	Leukopenia
12	Steroid-dependent	1.72	15	15	Pred 10 mg qd	Remission	NA	No

No., number

Pred, prednisone

MP, methylprednisolone

PCP, pneumocystis carinii pneumonia

VZV, varicella zoster virus

5-ASA, 5-aminosalicylic acid

Table 3 The occurrence of TPMT and NUDT15 genetic variants

Patient Number	Gene	RefSNP accession ID number	Variant	CPIC Allele	CPIC Allele Clinical Functional Status	CPIC Phenotype Summary	Adverse events
3	*NUDT15*	rs116855232	c.415 C>T (p.Arg139Cys)	*NUDT15*3*	No function	NUDT15 Intermediate Metabolizer	Mild leukopenia
10	*NUDT15*	rs116855232	c.415 C>T (p.Arg139Cys)	*NUDT15*3*	No function	NUDT15 Intermediate Metabolizer	None
11	*TPMT*	rs75543815	c.539 A>T (p.Tyr180Phe)	*TPMT*6*	Uncertain function	TPMT Indeterminate Metabolizer	Withdrawal for severe leukopenia
12	*NUDT15*	rs116855232	c.415 C>T (p.Arg139Cys)	*NUDT15*3*	No function	NUDT15 Intermediate Metabolizer	None

CPIC: Clinical Pharmacogenetics Implementation Consortium

Furthermore, *TPMT*6* was detected in patient 11, who took the dose of 2.04 mg/kg per day, and finally ceased the medication of AZA due to severe leukopenia. Functional statuses of these four heterozygous missense variants of *TPMT* and *NUDT15* identified in four patients were unknown.

Discussion

CCS is a quite rare disease with unfavorable prognosis as reported. The treatment of CCS is challenging on account of lack of cure medication and there is a big gap in the medication for steroid-dependent or steroid-refractory patients. AZA is one of old immunosuppressants which has been well prescribed in inflammatory bowel disease (IBD) and other autoimmune diseases. Our study retrospectively focused on the efficacy and safety of AZA in CCS patients. Firstly, AZA with the target dose of 1-1.5 mg/kg per day could be a good alternative medication for patients with steroid-dependent or refractory, and it could favor the clinical and endoscopic remission. Secondly, bone marrow suppression, opportunistic infection and liver dysfunction are major adverse events of AZA administered in CCS patients, especially in the first 2–3 months of medication. Thirdly, genotype analysis of *TPMT* and *NUDT15* helps to dose modulation of AZA.

Limited number of previous studies reported the usage of AZA in CCS patients. One study summarizing 103 CCS participants in China reported that 3.06% (3/103) of the participants took immunosuppressant agents [11], but the therapeutic roles have not been clarified. One small multicenter study in Japan reported a remission rate of 40% (2/5) among patients who received

azathioprine therapy over a period of 2 to 11 years [5], and another study showed that five patients who initially responded to corticosteroids maintained remission on azathioprine (2 mg/kg per day) after a median of 4.5 years [4]. The Mayo Clinic case series showed that 83.3% (10/12) of patients taking thiopurine therapy achieved steroid-induced remission during a median of 8.3 years of follow-up [12], which was similar to 80.0% of clinical remission in this study. However, the study did not address the target dose, duration of AZA medication, detailed adverse events and the genotypes of *TPMT* and *NUDT15* [12]. The consensus suggested that the standard dose of azathioprine be 2.0 to 2.5 mg/kg per day in IBD [8], while according to recent Asian studies, dose adjustments to 1.0 to 2.0 mg/kg per day may also be effective for steroid-dependent patients, with reduced risk of leukopenia than standard dose [13, 14]. In our cohort, the target dose of AZA was set at 1.0 to 1.5 mg/kg per day considering the older age and worse malnutrition status, which achieved the same sustained clinical remission. Considering the limited investigations concerning immunosuppressive therapy, the optimal treatment for CCS will require large-scale and long-term trials to clarify.

Adverse events associated with azathioprine included nausea, allergic reaction, pancreatitis, hepatotoxicity and an increased risk of lymphoma, of which myelotoxicity is the main concern about discontinuation. The CCS patients were elderly in the majority and frequently complicated with hypoalbuminemia, who carried an increased risk of infection and malignances, also challenging the clinical use of azathioprine. Although the risk of myelotoxicity is relatively high (4%) [15], titration therapy with low dose at onset and gradual dose increment may avoid the side effect as is dose-dependent. However, careful monitoring in administration of azathioprine took up to 6 months to attain therapeutic doses.

Furtherly, TPMT and NUDT15 genetic alleles characterized by diminished enzymatic activity are major cause of thiopurine-induced myelosuppression [10]. TPMT metabolizes thiopurine drugs to inactive forms, and thus diminished enzymatic activity of TPMT increases levels of active thioguanine (TGN) metabolites, which in turn increases the risk of hematopoietic toxicity [16]. NUDT15 converts TGNs to less-toxic metabolites and diminished enzymatic activity of NUDT15 will lead to accumulation of TGN. Compared with *TPMT* variants, *NUDT15* variants are more common in Asians and the primary genetic factor contributing to thiopurine-induced myelosuppression [17]. In our study, *NUDT15*3* was detected in three patients using sanger sequencing, only one of whom (patient 3) had mild leukopenia after AZA administration. The minor allele frequency of *NUDT15*3* in east Asian is 10.4345% [17]. It is associated with thiopurine-induced early leukopenia (odds ratio, 35.63; 95% confidence interval, 22.47–56.51). The median interval from the beginning of administration of AZA to leukopenia was 135 days (range, 12-3300) for patients with *NUDT15*1/*3* [18]. For patient 10 and patient 12 who carried the same allele, although leukopenia was not observed, closely monitoring is essential in the future. For patient 11 who had discontinued AZA due to severe leukopenia, one uncertain function allele (*TPMT**6) was detected. The functional status of this allele is uncertain and may account for leukopenia in this patient, although AZA dose of 2.04 mg/kg per day might also be considered. Overall, examination of *TPMT/NUDT15* allele status before azathioprine therapy could help to guide dose recommendations and lower the risk of leukopenia for CCS patients.

Unavoidably, this study has several limitations. First, it is the retrospective study concerning this rare disease, allowing for selection bias. Second, the number and follow-up duration of case series regarding therapy is relatively limited as a result of its rarity of the disease. Third, as mentioned above, the unavailability of *TPMT* and *NUDT15* allele test in routine clinical practice of our medical center brought trouble to the optimization of AZA use, which fortunately will be conducted routinely in our center before Dec 2024.

Conclusions

In conclusion, this retrospective study firstly examined the efficacy and safety of low-dose azathioprine (1.0 to 1.5 mg/kg per day) in Chinese CCS patients through long-term follow-ups, and azathioprine may be a good alternative for steroid-dependent or steroid-resistant patients. The severe adverse events associated with azathioprine included severe infection, leukopenia and liver dysfunction within the first 3 months, which might be partially avoided by conducting *TPMT* and *NUDT15* genotype as the routine laboratory test before prescribing AZA.

Abbreviations

CCS	Cronkhite-Canada syndrome
AZA	Azathioprine
GI	Gastrointestinal
CsA	Cyclosporine A
TPMT	Thiopurine methyltransferase
NUDT15	Nudix hydrolase 15
CPIC	Clinical Pharmacogenetics Implementation Consortium
PCP	*Pneumocystis carinii* pneumonia
IBD	Inflammatory bowel disease
TGN	thioguanine

Supplementary Information

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Supplementary Material 1

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Author contributions
QSX, LXJ and CZO contributed equally to this work and should be considered as co-first authors; QSX, LXJ and CZO contributed to acquisition of data, analysis and interpretation of data, drafting and revision of the manuscript; TMX, ZY, RFZ, SL, XMY and GCR contributed to patient enrollment, revision of the manuscript for clinical content; JL contributed to study concept and design, study supervision, acquisition of data, conducting colonoscopy procedures, analysis and interpretation of data, drafting and revision of the manuscript; JNL contributed to study supervision, acquisition of data, critical revision of the manuscript for important intellectual content and All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from each patient, and this study was approved by the Institutional Review Board of Peking Union Medical College Hospital (I-22PJ1077).

Consent for publication
All individuals provided consent for publication as part of the informed consent process.

Competing interests
The authors declare no competing interests.

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