Association of *NUDT15* gene polymorphism with adverse reaction, treatment efficacy, and dose of 6-mercaptopurine in patients with acute lymphoblastic leukemia: a systematic review and meta-analysis

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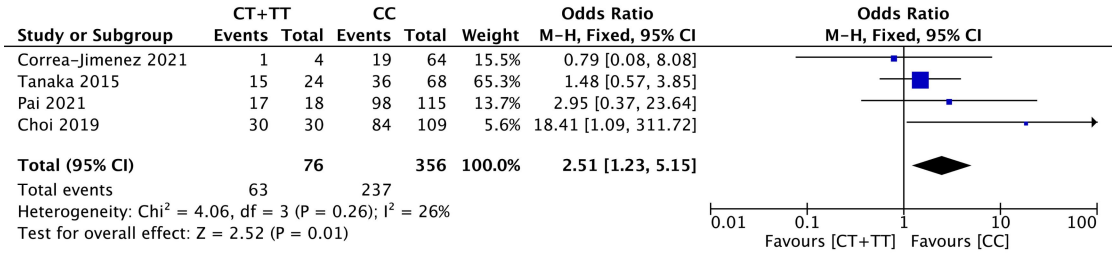

Figure S1. The forest plots for the meta-analysis of association of *NUDT15* c.415C>T (rs116855232) with 6-MP treatment interruption in the dominant model excluding the study Zhou.

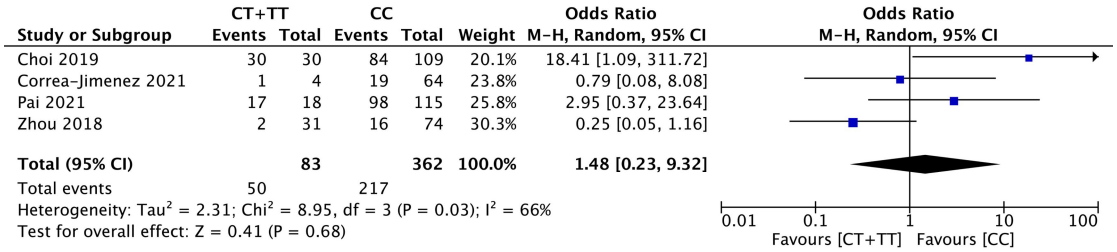

Figure S2. The forest plots for the meta-analysis of association of *NUDT15* c.415C>T (rs116855232) with 6-MP treatment interruption in the dominant model with the same initial dose.

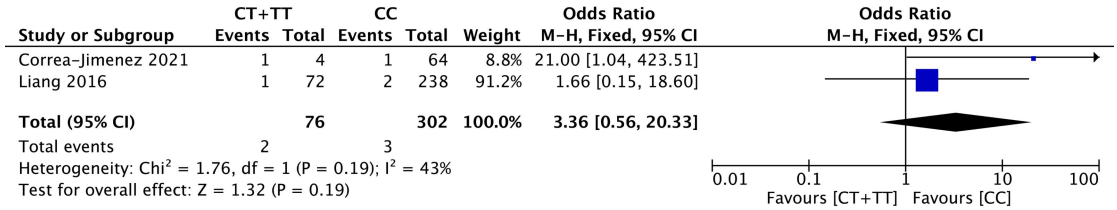

Figure S3. The forest plots for the meta-analysis of association of *NUDT15* c.415C>T (rs116855232) with death of ALL patients treated with 6-MP in the dominant model.

Table S1 Definition of ADR, standard of 6-MP dose adjustment and 6-MP interruption

Study	Definition of ADR	Initial dose ($mg/m^2/d$)	6-MP dose adjustment	6-MP interruption
Buaboonnam 2019	Neutropenia: ANC <500/μL	Maintenance:50	1. maintain ANC 500-1,500/μL 2. Those who had a second episode or more of neutropenia and thrombocytopenia received 50% of the standard dose of 6-MP to maintain ANC >750 /μL and PLT >75 000 /μL, with the exception of those who had neutropenia secondary to an intercurrent viral infection. This latter group continued to receive the previous dose without reduction. 3. Those with ANC >1,500 /μL for 2 consecutive months received a 25% dose increase of either 6-MP or MTX, after which these medications were increased alternately if ANC was maintained >1,500 /μL	ANC <500 /μL or PLT <50×10^3/μL
Cao 2020	Leukopenia: NA	remission induction stage (60), consolidation stage (25), and maintenance stage (50)	1. remission induction: planed 6-MP: 60 mg/m^2/d po qn d29-35, if d33 WBC <2.0×10^3/μL or ANC <0.8×10^3/μL reduce 50% of 6-MP 2. maintenance: to maintain WBC (1.8~3.0) $\times10^3$/μL, and ANC (0.5~1.2) $\times10^3$/μL and PLT ≥50×10^3/μL 3. direct bilirubin 24~51μmol/L, reduce 50% of 6-MP; 51~85 μmol/L, reduce 75%	1. consolidation: ANC <0.5×10^3/μL or WBC <1.5×10^3/μL or PLT < 50×10^3/μL 2. maintenance: ANC <0.5×10^3/μL or WBC <2×10^3/μL or PLT <50×10^3/μL 3. ALT≥10ULN or direct bilirubin≥85 μmol/L
Chiengthong 2016	Neutropenia: ANC <500/μL	Maintenance:50	6-MP was either increased by 25% of the previous dose or discontinued, to keep ANC 500-1,500 /μL	6-MP was either increased by 25% of the previous dose or discontinued, to keep ANC 500-1,500 /μL
Choi 2019	Leukopenia: WBC <1.5×10^3 /μL Neutropenia: ANC <500/μL Interruption: when patients showed significant hematopoietic toxicity	Maintenance:50	if WBC is out of the range ($1.5\sim3\times10^3$ /μL) and 6-TGN levels were out of therapeutic range (235-450 pmol/8×10^8 RBC)	1. significant hematopoietic toxicity (ANC< 0.5×10^3/μL or PLT< 50×10^3/μL) 2. serious infectious events.
Correa-Jimenez 2021	Neutropenia: NA	Maintenance:50	WBC 1000-2000/μL, MP/MTX dose 50%; WBC >2,000-3,000/μL, MP/MTX dose 100%; WBC >3,000/μL, MP/MTX dose up to 150%; Lymphocytes <300/μL, MP/MTX dose 50%	1. WBC<1,000/μL; 2. Infections; 3. Grade≥3 liver toxicity (ALT/AST>5×ULN for age; Bilirubin>3× ULN for age); 4. Long-standing diarrhea
Fan 2022	Hepatotoxicity: ALT >500 U/L	Maintenance:50	NA	NA
Khaeso 2022	Neutropenia: ANC <500/μL	Maintenance:50	maintain ANC >750/μL and PLT > 75,000 /μL	the 6-MP dose was adjusted or 6-MP dose interruption was performed based on the clinician's judgement every month
Khera 2019	Neutropenia: ANC <750/μL	Maintenance:60	maintain an ANC between 750-1500/μL	NA
Kim 2018	Neutropenia: ANC <500/μL	Maintenance:50	maintain WBC (2.0-3.5) $\times10^3$/μL and ANC>500/μL	NA
Li 2021	Leukopenia: WBC <2.0×10^3 /μL Neutropenia: ANC <1000/μL	Maintenance:50	1. maintenance: to maintain WBC (1.8 ~3.0) $\times10^3$/μL, and ANC (0.5~1.2) $\times10^3$/μL, and PLT≥50×10^3/μL 2.direct bilirubin 24~51μmol/L, reduce 50% of 6-MP; 51~85 μmol/L, reduce 75%	1. maintenance: ANC<0.5×10^3/μL or WBC<2×10^3/μL or PLT <50×10^3/μL 2. ALT≥10 ULN or direct bilirubin≥85 μmol/L
Liu 2018	Leukopenia: WBC≤2.0×10^3 /μL	Maintenance:50	maintain WBC about 3×10^3/μL, and ANC (1.0~1.5) $\times10^3$/μL	NA
Mao 2021	Leukopenia: WBC <2.0×10^3 /μL Hepatotoxicity: ALT or AST >5-fold of normal	Maintenance:50	maintain WBC (2.0-3.0) $\times10^3$/μL	NA

Moradveisi 2019	Hepatotoxicity: the highest direct bilirubin values ≥1.5 mg/dL	Maintenance:75	maintain WBC (2.0-3.0) $\times 10^3/\mu L$	NA
Pai 2021	Neutropenia: ANC <1500/μL Interruption: cessation of medicine administration resulting from cytopenia, infections, or hepatotoxicity.	Maintenance:50	maintain WBC >3.0 $\times 10^3/\mu L$	1. hepatotoxicity: ALT/AST >5.0-20.0 × ULN if the baseline was normal; >5.0-20.0 × baseline if the baseline was abnormal at any time point during maintenance therapy 2. severe myelotoxicity/neutropenia: ANC < 500/μL 3. infections
Tanaka 2015	Leukopenia: WBC $<2.0\times10^3$ /μL Hepatotoxicity: ALT >700 IU /L Interruption: the cessation of the administration of treatment resulting from any adverse events	Maintenance:40	maintain WBC (2.0-3.5) $\times 10^3/\mu L$	WBC$<2\times10^3$ /μL or ALT>700 IU/L
Tanaka 2018	Leukopenia: WBC $<2.0\times10^3$ /μL Hepatotoxicity: ALT >700 IU /L	Maintenance:40	maintain WBC (2.0-3.5) $\times 10^3/\mu L$	WBC$<2\times10^3$ /μL or ALT>700 IU/L
Wang 2022	Neutropenia: ANC <500/μL	Maintenance:50	if ANC $<0.5\times10^3/\mu L$, 6-MP reduces 25%～50%	ANC$<0.2\times10^3/\mu L$
Wang 2021	Hepatotoxicity: either ALT or AST or ALP or TBIL is more than 2 ULN	Maintenance:50	NA	NA
Zhou 2018	Leukopenia: WBC $<2.0\times10^3$ /μL Hepatotoxicity: ALT or AST>500 U/L Interruption: the cessation of the administration of medicine resulting from infections and/or hepatotoxicity	Maintenance:50	6-MP was either increased or decreased by 50% of the previous dose or even discontinued to maintain WBC (2.0-3.0) $\times 10^3/\mu L$	1. infections 2. ALT or AST > 500 U/L
Zhu 2018	Leukopenia: NA Hepatotoxicity: more than 5 times of increased ALT and/or AST	remission induction stage (60), consolidation stage (25), and maintenance stage (50)	1.remission induction: planed 6-MP: 60 $mg/m^2/d$ po qn d29-35, if d33 WBC $<2.0\times10^3/\mu L$ or ANC $<0.8\times10^3/\mu L$ reduce 50% of 6-MP 2. maintenance: to maintain WBC (1.8 ~3.0) $\times10^3/\mu L$, and ANC (0.5~1.2) $\times10^3/\mu L$ and PLT $\geq50\times10^3/\mu L$ 3.direct bilirubin 24~51μmol/L, reduce 50% of 6-MP; 51~85 μmol/L, reduce 75%	1. consolidation: ANC $<0.5\times10^3/\mu L$ or WBC $<1.5\times10^3/\mu L$ or PLT< 50 $\times10^3/\mu L$ 2. maintenance: ANC $<0.5\times10^3/\mu L$ or WBC $<2\times10^3/\mu L$ or PLT <50 $\times10^3/\mu L$ 3. ALT ≥10 ULN or direct bilirubin≥85 μmol/L

Abbreviations: 6-MP, 6-mercaptopurine; ADR: adverse drug reaction, including leukopenia, neutropenia, hepatotoxicity and interruption; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; MTX, methotrexate; NA, not available; PLT, platelet; TBIL, total bilirubin; ULN, upper limit of normal; WBC, white blood cell.