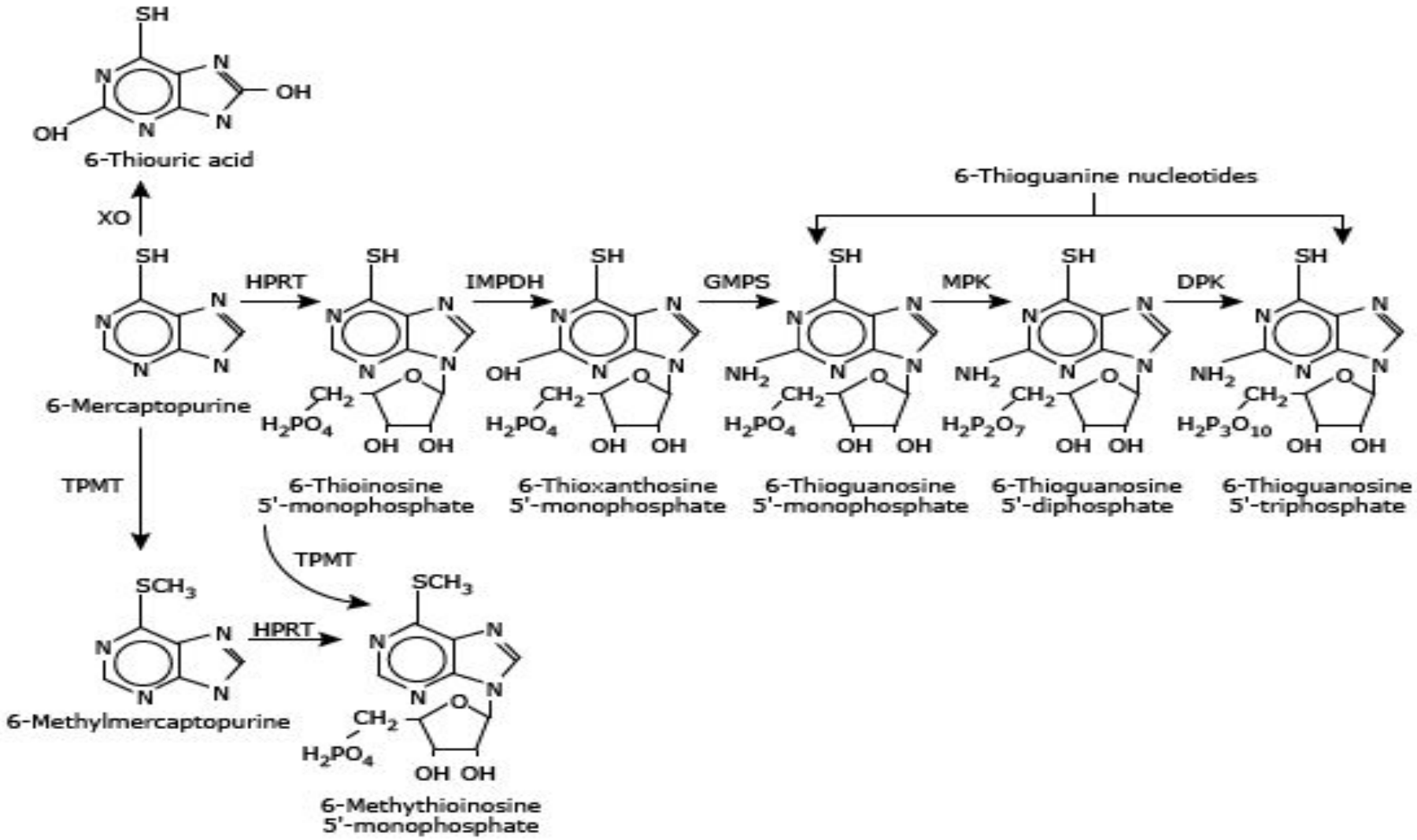
TPMT testing in patients with inflammatory bowel disease

The therapeutic efficacy, bone marrow toxicity, and liver toxicity of (AZA) and (6-MP) may be related to their metabolites: 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP

AZA is metabolized to 6-MP, then to 6-TG and 6-MMP.

Two enzymes are responsible for catalyzing these reactions: thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase (HPRT)


6-Thiouric acid
XO
6-Thioguanine nucleotides
6-Mercaptopurine
HPRT
IMPDH
GMPS
MPK
DPK
6-Thioinosine 5'-monophosphate
6-Thioxanthosine 5'-monophosphate
6-Thioguanosine 5'-monophosphate
6-Thioguanosine 5'-diphosphate
6-Thioguanosine 5'-triphosphate
TPMT
TPMT
6-Methylmercaptopurine
HPRT
6-Methythioinosine 5'-monophosphate

6-TG levels between 230 and 400 response and remission of IBD .

Bone marrow suppression may correlate with 6-TG greater than 400,

elevated levels of 6-MMP levels greater than 5700 may correlate with liver toxicity.

TPMT ENZYME DETERMINATION

(TPMT) genotype and TPMT enzyme activity (phenotype) testing in all patients who are evaluated for treatment with (AZA) or (6-MP).

Approximately 89 percent of the population has normal or "high" TPMT enzyme activity

11 percent have low TPMT enzyme activity.

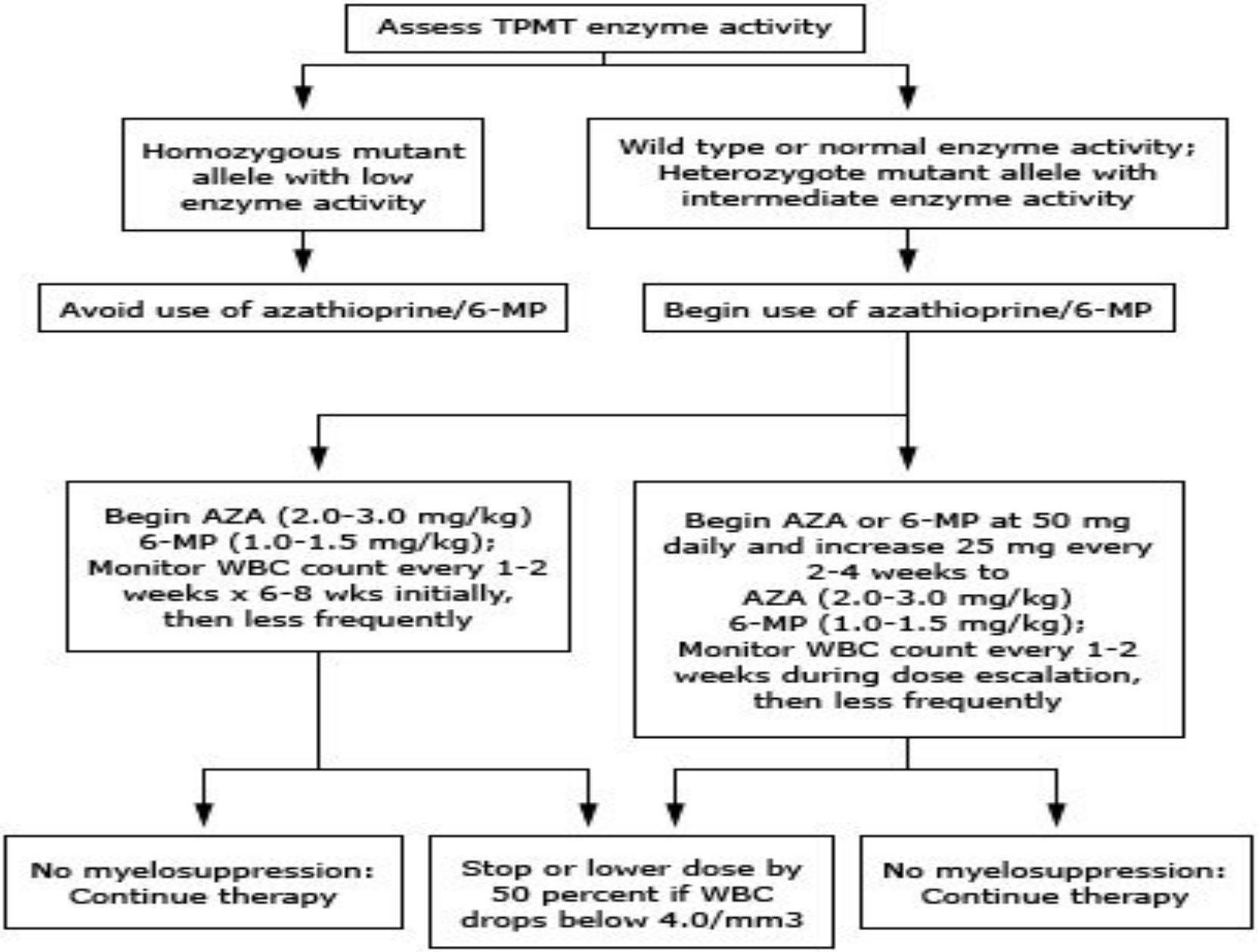
0.3 percent (1 in 300) of the population have negligible activity .

TPMT enzyme activity (phenotype) can be measured

Those with absent TPMT enzyme activity should not receive azathioprine or 6-mercaptopurine.

Those with low (<5 unit/mL) enzyme activity can be treated with low-dose

TPMT enzyme activity between 5 to 12 unit/mL may be more likely to respond to a more moderate dosing


Assess TPMT enzyme activity
Homozygous mutant allele with low enzyme activity
Wild type or normal enzyme activity; Heterozygote mutant allele with intermediate enzyme activity
Avoid use of azathioprine/6-MP
Begin use of azathioprine/6-MP
Begin AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg); Monitor WBC count every 1-2 weeks x 6-8 wks initially, then less frequently
Begin AZA or 6-MP at 50 mg daily and increase 25 mg every 2-4 weeks to AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg); Monitor WBC count every 1-2 weeks during dose escalation, then less frequently
No myelosuppression: Continue therapy
Stop or lower dose by 50 percent if WBC drops below 4.0/mm3
No myelosuppression: Continue therapy

TPMT activity may require repeated measurements since 6-mercaptopurine and azathioprine can induce an increase in TPMT activity.

5-ASA drugs, for example, can reversibly inhibit TPMT activity

Allopurinol inhibits the enzyme xanthine oxidase and should be avoided,

Routine laboratory testing

complete blood count and liver chemistries at least every other week for six to eight weeks

Then everythree months thereafter .

Therapeutic drug monitoring

several studies have demonstrated that therapeutic efficacy correlates with concentrations of 6-thioguanine (6-TG) between 230 and 400.

bone marrow suppression correlates with concentrations of 6-TG greater than 400

cont

liver toxicity correlates with concentrations of 6-methylmercaptopurine (6-MMP) greater than 5000.

No correlation was found between therapeutic efficacy and 6-MMP levels.

Following 6-TG and 6-MMP

for optimal dosing of AZA or 6-MP.

predict toxicity AZA or 6-MP.

non-compliance or resistance

Low or absent 6-TG levels in non-responding patients may

indicate noncompliance

, use of a sub-therapeutic dose of AZA/6-MP, or preferential metabolism to 6-MMP instead of 6-TG (ie, 6-MP resistance).

SUMMARY AND RECOMMENDATIONS

We suggest (TPMT) genotype and TPMT enzyme activity (phenotype) testing in all patients

complete blood count and liver chemistries at least every other week for six to eight weeks and at least once every three months thereafter

SUMMARY AND RECOMMENDATIONS

In patients who previously developed leukopenia or elevated liver biochemical tests while taking 6-MP or AZA, we suggest obtaining not only TPMT genotype testing and TPMT enzyme activity, but also 6-MP metabolite testing….

A normal TPMT screening test does not preclude bone marrow and/or liver toxicity.

SUMMARY AND RECOMMENDATIONS

patients with high TPMT activity may be predisposed to forming potentially hepatotoxic levels of 6-methylmercaptopurine (6-MMP).

Monitoring of the CBC and liver function tests weekly for the first month and then monthly must be continued .

شكرا جزيلا