Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites

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The current U.K. trial protocol (UKALL XI) for childhood lymphoblastic leukaemia demands mercaptopurine (MP) dose escalation in children who tolerate daily 75 mg/m² MP (100% dose) without cytopenias. The previous trial (UKALL X) did not. MP metabolism was studied in a group of UKALL XI children (*n*=21) who tolerated 100% dosages and who were matched in this respect with a similar group of UKALL X children. Red blood cell MP derived thioguanine nucleotide (TGN) concentrations were measured in both groups under comparable conditions; at 75 mg/m² MP there was no significant difference. MP dose escalation in the UKALL XI children produced higher TGN concentrations (TGNs at 100% *vs* 125% dosages, median difference 90 pmol/8 × 10⁸ RBCs, 95% CI 25 to 165 pmol, *P*<0.02). Assayed at the time of cytopenia induced dose reduction, the UKALL XI children had accumulated significantly higher TGN concentrations than the UKALL X children (median difference 78 pmol/8 × 10⁸ RBCs, 95% CI 20 to 144, *P*<0.02). These findings indicate that dose escalation in children tolerant of 100% MP dosages produces higher peak TGN concentrations.

Keywords childhood leukaemia thioguanine nucleotides mercaptopurine compliance

Introduction

Mercaptopurine (MP) is universally used in the continuing chemotherapy of standard risk 'acute' lymphoblastic leukaemia (ALL) in children. The anti-leukaemic effect of MP can be related to drug derived thioguanine nucleotides (TGNs) [1]. Children vary in their ability to produce TGNs, and those who fail to form adequate amounts are at an increased risk of disease relapse [1, 2]. For children who tolerate 75 mg/m² MP without cytopenias the current UK trial for ALL (UKALL XI) includes a cycle of MP dose escalation, whereas the previous trial (UKALL X) did not [3]. Such dose escalation has not led to an increase in the cumulative dose of MP prescribed because it generates more gaps in treatment due to more frequent drug withdrawal [4]. We were concerned that the gaps in therapy produced by escalation might paradoxically reduce the cytotoxicity of MP, so were interested to see what effect escalation

had on TGN concentrations. To find out we compared two consecutive cohorts of children who were treated according to UKALL X and UKALL XI respectively.

Methods

Consecutive eligible children with ALL who received continuing chemotherapy according to UKALL XI, and who could tolerate 75 mg/m² MP for over 4 weeks, were studied. We compared them with group of UKALL X children matched for order of diagnosis, MP tolerance and gender. Sex-matching was considered important because on similar prescribing criteria boys tolerate more MP than girls [4].

Daily oral MP therapy was similar in both trials with a standard dose of 75 mg/m² (100% MP). The children underwent protocol directed dose attenuation in

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response to neutropenia and/or thrombocytopenia. The UKALL XI children differed in that if 100% MP was tolerated for 4 consecutive weeks it was increased to 125% standard dose, and then monthly in further increments of 25% until cytopenia was induced.

Blood samples for the measurement of red blood cell (RBC) TGNs were obtained after at least 2 months of MP therapy when MP had been prescribed at the standard 100% dose or higher for at least the preceding 7 days, and when at least 2 months had elapsed since a RBC transfusion or a 5-day 'block' of intensive therapy [3]. All patient procedures were approved by the local Ethics Committee.

RBC TGNs were measured as previously described [5]. The lower limit of reproducibility was 30 pmol/ 8×10^8 RBCs (interassay coefficient of variation 5.8%). Medians were compared by the Mann-Whitney test.

Results

Four children (two from each trial) were not eligible for the study. They could not tolerate 100% $\times$ 4 weeks MP. TGN concentrations at their maximum MP dosage ranged from 500 to 1140 pmol/ 8×10^8 RBCs. Twenty-one UKALL XI children (7 girls and 14 boys) were studied. From them 139 TGN assays were obtained at 100% MP (median 6 per child) and 104 assays at 125% (median 5 per child). TGNs were compared in the first 100 to 125% escalation cycle (one reading per child). The TGN range at 100% was 113–520, and at 125% 135–637 pmol/ 8×10^8 RBCs with a median difference of 90 pmol (95% CI = 25 to 165 pmol, $P < 0.02$).

Eleven children required titration to 150% at some point in the study, three to 175% and one to 200%. The three children titrated beyond 150% MP had lower TGN concentrations at higher doses than at 100% dose. One child had TGN concentrations at 200% dosages half those recorded at 125% MP. Partial compliance was suspected, and admitted in one case.

The UKALL XI children were then compared with a group of 21 UKALL X children who tolerated 100% MP for 4 weeks or more. The UKALL X children had a total of 99 assays (median 5 per child) at 100% MP. The UKALL XI children spent a median of 37% of their time on cytopenia induced MP dose reduction or

withdrawal whereas the figure for UKALL X children was 27% (median difference 7.5%, 95% CI—1.4 to 14%, $P = 0.09$). Cytopenia-driven dose reductions were more frequent in the UKALL XI children, but this did not reach significance [4].

There was no difference in TGN concentrations between UKALL XI or X taking either a single assay per child (the first), or the median value of all 100% assays for each child. There was a difference if just the TGN assays taken at the time cytopenia occurred were considered. For the UKALL X children 56 such assays were available (median 3 per child) and for the UKALL XI children 74 (median 4 per child). Comparison of the median values gave a difference of 78 pmol (95% CI 20 to 144 pmol, $P < 0.02$) (Table 1). The UKALL XI children had accumulated significantly higher concentrations of TGNs at the stage when their blood counts dropped.

Discussion

Continuing 'maintenance' chemotherapy is an important component of successful ALL protocols [1, 6] and MP dose escalation is an attempt to avoid inadvertent under-treatment. Our findings provide some reassurance that, even if it produces more gaps in an ideally continuous schedule [4], escalation produces greater peaks in intracellular TGN concentrations which could translate into greater efficacy due to the long half life of such metabolites [1]. Whether that hope is realised remains to be seen.

It is worrying that three children on escalated MP doses ($> 150\%$) had lower metabolite assay values at higher MP doses than at lower dosages and we regard this as evidence of partial compliance. This was admitted by one child. There are many other possible reasons for variation in intracellular metabolites, and we acknowledge that our suspicions are based on circumstantial evidence. Recognition of non-compliance is very important because if non-compliant children suddenly start to take an inflated dose they could suffer profound myelosuppressive toxicity.

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Table 1 A comparison of TGN concentrations (range (median)) in UKALL X and XI

	TGN (pmol/ 8×10^8 RBCs)		
	First assay at 100% MP	Median of all 100% assays	Median of all assays at time of dose reduction
UKALL X	156 to 629 (323)	156 to 545 (317)	246 to 503 (317)
UKALL XI	113 to 520 (317)	116 to 536 (293)	270 to 643 (385)
Median difference	24	26	78 (95% CI = 20 to 144)
Two-tail $P =$	0.46	0.41	0.017

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