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SHORT COMMUNICATION

Jennifer C. Welch · John S. Lilleyman

6-Mercaptopurine dose escalation and its effect on drug tolerance in childhood lymphoblastic leukaemia

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Abstract Daily oral 6-mercaptopurine (6MP) is important in the treatment of childhood lymphoblastic leukaemia (ALL), but there is great inter-patient variability in the pattern of evident drug effect (myelosuppression) seen at a standard dose. In an attempt to reduce that variability the current practise in the United Kingdom for the last 4 years has been to escalate the amount prescribed in patients who do not experience cytopenias at 75 mg/m^2. We undertook a study to see whether that strategy would increase the total dose of 6MP prescribed in such patients and whether it would alter the pattern of myelosuppression. Over a 6-month period we studied 44 children treated conventionally (without escalation) and compared them with another 44 (matched for sex) who were treated on the same protocol but where doses were increased in monthly 25% steps if 75 mg/m^2 was tolerated without cytopenias. We then compared the two groups for the total dose of drug prescribed and the frequency and duration of neutropenia or throrabocytopenia. The median cumulative dose of 6MP received by the conventionally treated children (10,002 mg/m^2) was not significantly different from that of the children treated with dose escalation (9,429 mg/m^2). In a comparison of the 30 children who actually received inflated doses of 6MP with the 37 from the conventional cohort who would have been eligible to do so, it was again found that the cumulative median doses were similar (10,460 versus 10,916 mg/m^2). There *was* a difference between the two groups in the pattern of myelosuppression — the escalated group spent significantly more time off 6MP than did the non-escalated group (median 4.5 versus 3 weeks; $P < 0.005$, 95% CI from -1 to -3). These findings imply that the method of dose escalation employed does not allow more 6MP to be prescribed in children tolerant of the standard dose. The chief effect seems to be to generate longer periods off therapy, and this could paradoxically decrease the anti-neoplastic activity of the drug. Alternative ways of prescribing should be explored.

Key words Lymphoblastic leukaemia · 6-Mercaptopurine · Myelosuppression

Introduction

Children taking 6-mercaptopurine (6MP) who produce low concentrations of intra-cellular cytotoxic metabolites during continuing (maintenance) therapy for lymphoblastic leukaemia (ALL) may be more likely to relapse [7]. Such patients also experience less myelosuppression. In view of this these observations the current protocol in the United Kingdom is to escalate the dose of maintenance 6MP in those children who do not experience neutropenia or thrombocytopenia after 4 weeks at the conventional standard dose of 75 mg/m^2, and the only limit to the 6MP dose is eventual marrow toxicity. It is thought that by titrating upwards in this way, children peculiarly tolerant of 6MP may have the opportunity to form higher concentrations of cytotoxic metabolites and, thus, to have a more reliable drug effect. Prior to this modification of treatment there was no provision for increasing the 6MP dose beyond the standard 75 mg/m^2, even if children could tolerate it for long periods without cytopenias [3].

Thus, far the effect of the strategy has not been assessed. Although it will be some time before any

J. C. Welch (✉)
University of Sheffield, Department of Paediatrics,
Section of Paediatric Haematology, The Children's Hospital,
Sheffield S10 2TH, UK

J. S. Lilleyman
Academic Department of Paediatric Oncology, St. Bartholomew's Hospital, London EC1A 7BE, UK

influence on outcome is likely to become apparent, and although presently there are insufficiently detailed data on drug metabolite concentrations in a large enough group of children, there is enough experience to examine the change, if any, in the amount of drug prescribed and the pattern of toxicity. With this in mind we studied a group of children treated without dose escalation and compared them with a more recent group where the dose was limited only by neutropenia or thrombocytopenia.

Patients and methods

Recruiting patients from two regional cancer centres we examined two cohorts of children, one treated before 1990 and one treated after that date. The early group was a consecutive series of children with ALL who reached 18 months from diagnosis in their first remission. At that stage they had all received remission induction therapy followed by none, one, or two intensification blocks of chemotherapy (see Table 1). They then followed a conventional protocol for 6MP dosage as part of remission maintenance therapy [3]. Briefly, the plan was to start at the standard dose of 75 mg/m^2, to reduce the dose to 50% at a neutrophil threshold of $\langle 1.0 \rangle 0.5 \times 10^9$/l or a platelet threshold of $\langle 100 \rangle 50 \times 10^9$/l, and then to resume at 75% for 2 weeks prior to the full dose once the counts were back over the thresholds. If counts fell to $< 0.5 \times 10^9$/l (neutrophils) or $< 50 \times 10^9$/l (platelets), 6MP was withdrawn until they recovered to > 1.0 and $> 100 \times 10^9$, respectively, whereupon the dose was re-introduced at 50% for 1 week and then at 75% for 2 weeks before resumption of the full 75 mg/m^2. Weekly oral methotrexate (standard dose 20 mg/m^2) was adjusted in parallel.

The later group was a similar cohort of children selected only to match the first group for gender. This was because boys tolerate more 6MP than do girls on similar prescribing criteria [5, 7]. Early therapy differed slightly for this group in that all children had received two intensification blocks of chemotherapy and half had (randomly) received a third block (see Table 1). The maintenance treatment they had was the same as that received by the early group, with 6MP dose escalation being the only difference. The pattern of escalation was simple. The standard protocol dose of 6MP (75 mg/m^2) was increased by 25% if tolerated for 4 weeks without neutropenia or thrombocytopenia occurring. A further stepwise increase of 25% in the dose occurred at monthly intervals until myelosuppression (a drop in the neutrophil or platelet count) necessitated a dose reduction. When cytopenia occurred, the dose was reduced to 0 or 50% of the original target dose and then re-introduced as in the early group following count recovery. Each child (both groups) was studied over the same 6-month period of their therapeutic schedule — the 26 weeks following the first anniversary of the start of therapy.

Table 1 Number of intensive chemotherapy blocks received prior to the study period

	Number of "intensive" blocks of chemotherapy			
	0	1	2	3
No escalation group ($n = 44$)	17	14	13	0
Potential escalation group ($n = 37$)[a]	12	12	13	0
Escalation group ($n = 44$)	1	1	26	16
Actual escalation group ($n = 30$)[b]	0	0	17	13

[a] Children in the earlier cohort who did not receive dose escalation but would have qualified to do so following the current criteria
[b] Children in the "escalation group" who actually received doses of 6MP above 75 mg/m^2 on at least one occasion

Data were obtained from case records and chemotherapy prescription charts. The total dose of 6MP prescribed over the 26 weeks for each child was calculated in milligrams per square meter of body surface area. The two groups were analysed in their entirety, and then sub-groups from each cohort defined on the basis of whether they actually received (later group) or potentially would have been eligible to receive (early group) escalated doses were studied.

Median values for the variables studied in the two groups were assessed for significance using the Mann-Whitney U-test. It was calculated that the number of patients studied gave us an 85% chance of detecting a 15% difference in the cumulative dose [1].

Results

A total of 88 children were studied, 44 without dose escalation (early group) and 44 with escalation (later group). Overall, 37 children from the early group would have qualified for inflated doses had they been in the later group, and 30 in the later group actually received more than the standard dose on at least 1 occasion.

The total dose of 6MP prescribed was not significantly different over the period studied between the early and later groups (median 10,002 versus 9,429 mg/m^2; $P = 0.53$, 95% CI -621 to $+1{,}147$). When just the 67 tolerant children were reviewed, no difference in the cumulative dose was detectable between the 37 in the early group and the 30 in the later group (10,308 versus 10,556 mg/m^2; $P = 0.56$, 95% CI -1325 to $+725$).

There was, however, a difference in the pattern of myelosuppression. The number of weeks for which 6MP had to be stopped due to neutropenia or thrombocytopenia was significantly greater for those in the later group than for those in the early group (median 4.5 versus 3 weeks; $P = 0.003$, 95% CI from -2 to -1). The same was also true for the 67 tolerant children (median 4 versus 2 weeks; $P = 0.01$, 95% CI from -2 to 0). The results are shown in Table 2.

We considered whether more intensive earlier therapy had influenced the second (later) group's ability to tolerate subsequent chemotherapy. Separate subgroups were analysed as follows: children from both cohorts who had received 2 intensification blocks and received ($n = 17$) or potentially would have received ($n = 13$) inflated doses were compared and, again, there was no significant difference in the cumulative dose of 6MP prescribed (median 9,814 mg/m^2 for the non–escalated group versus 10,383 mg/m^2 for the escalated children; $P = 0.86$). There was more myelosuppression in the

Table 2 Myelosuppression and cumulative dose of 6-mercaptopurine; Median doses are given in mg/m^2 and ranges are shown in parentheses

	Number (whole group)	Cumulative 6MP dose	Weeks at 0	Weeks at maximum	Weeks at reduced dose	Number in > 100% group	Cumulative 6MP dose (> 100% group)	Weeks at 0 (> 100% group)	Weeks at maximum (> 100% group)	Weeks at reduced dose (> 100% group)
No escalation group	44	10,002 (3983.8–13,973.4)	3 (0–13)	12.5 (0–26)	13.5 (0–26)	37	10,308 (7,568–13,973.4)	2 (0–7)	3 (6–26)	12.8 (0–20)
Escalation group	44	9,429 (6,092.8–18,475.7)	4.5 (0–9)	11 (3–24)	14 (2–23)	30	10,556 (7,686.7–18,475.7)	4 (0–7)	13 (3–24)	12.75 (4–23)

escalated group (median 4 weeks at a percentage of 0 versus 2 weeks; $P = 0.005$, 95% CI 1.0–3.6). A comparison was also made of those children on escalated doses who had received 3 intensification blocks ($n = 13$) and those in the earlier cohort who had received either none or 1 block ($n = 24$). The median cumulative doses were 11,154 and 10,426 mg/m^2, respectively ($P = 0.45$). The median time spent at a dose percentage of 0 was 3.0 weeks for the escalated, 3-intensification-block children and 2.5 weeks for the 0- or 1-intensification-block group ($P = 0.52$).

In both groups, boys were prescribed more 6MP than were girls (10,304 versus 9,360 mg/m^2 in the early group and 10,880 versus 8,635 mg/m^2 in the later group). This reached statistical significance in the later cohort ($P = 0.005$, 95% CI 614–3,291).

Discussion

6MP is important in the successful management of childhood ALL and is universally used as a major component of so-called remission "maintenance" treatment. Exactly how and why prolonged continuing daily therapy is effective in this particular malignant disease is less clear than the simple observation that it is [4]. In recent years, much attention has been paid to the pharmacology of 6MP [2, 8], but despite that it must be admitted that we nonetheless do not know the best way to give this important agent. The traditional continuous daily low-dose oral therapy has been compared with pulse intermittent therapy or treatment given for 3 of 4 weeks [9], and present trials are exploring the value of giving 6MP intravenously, but there is currently no convincing evidence that any schedule is more effective than continuous low-dose treatment.

Cytotoxic metabolites derived for 6MP accumulate within cells over a period of days and disappear on a similar time scale once the drug has been withdrawn [6]. Measurement of these metabolites can thus give some indication of the adequacy of therapy, and it is probable that the concentration of intracellular metabolites relates to the likelihood of relapse [7].

Many factors affect the concentration of drug metabolites in cells, and these are only now being tentatively explored. For oral 6MP these include compliance, absorption, transport and intra-cellular metabolism. Based on the assumption that many of these variables (other than compliance) might be circumvented if doses for individual children were tailored to their response in terms of myelosuppression, the current practise in the United Kingdom was adopted, whereby the dose of 6MP is escalated in patients who do not develop cytopenias at the standard dose of 75 mg/m^2 for more than 4 weeks. The idea was that by increasing the dose until myelosuppression occurred, it would be more likely that an adequate cytotoxic effect would be achieved.

The findings described herein throw some doubt on whether this ambition has been realised. We recognise that the use of historical controls is a weakness in our study design, particularly as the intensity of early therapy differed in the two cohorts we compared, but there was nothing to suggest that the recipients of three intensification "blocks" were less tolerant than the children who had received none or one block. Thus, we conclude that in the patients we studied, escalating the doses did not increase the overall amount of 6MP taken, as it led to an increased period of drug withdrawal. Therapy thus became effectively intermittent with a similar cumulative dose, and previous experience indicates that, dose for dose, intermittent treatment may be less effective than continuous treatment. It is therefore possible that the anti-leukaemic effect of 6MP will not be improved by the prescribing practice of titrating to toxicity in the way currently practised in the United Kingdom.

An alternative view would be that the same cumulative dose is being given more effectively as it results in more cytopenic episodes. The breaks in treatment cannot be directly compared with previous "intermittent" therapy as the gaps are drug effect-induced by the cytotoxicity of the 6MP. Hence, despite its intermittent nature, escalated therapy may prove to be more

effective. Until we have longer follow-up periods and good data on intra-cellular metabolite concentrations the question will remain unsolved.

Either way, simply to revert to the old system of a standard ceiling target dose of 75 mg/m^2 is not an option. It will not solve the problem of the child who may be truly tolerant of 6MP. Such patients could have the dose tailored to their (regularly measured) intracellular metabolite concentrations, or some other schedule of dose adjustment could be explored, or both of these approaches could be used. It may be that the increments of 25% are too great or, more likely, it may be that our method of cautiously re-introducing the drug at 50% and 75% of the standard target dose over 3 weeks is unnecessarily timid. We are not aware of any study showing that re-introduction of 6MP at attenuated doses following recovery from a period of cytopenia is necessary. Perhaps all we can be certain of is that despite many years of experience, we are still some way from establishing the best method to prescribe 6MP for maintenance treatment of ALL.

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