Individualized toxicity-titrated 6-mercaptopurine increments during high-dose methotrexate consolidation treatment of lower risk childhood acute lymphoblastic leukaemia. A Nordic Society of Paediatric Haematology and Oncology (NOPHO) pilot study

Thomas L. Frandsen, Jonas Abrahamsson, Birgitte Lausen, Kim Vettenranta, Mats Heyman, Michael Behrentz, Anders Castor, Peder S. Wehner, Britt-marie Frost, Elisabeth W. Andersen and Kjeld Schmiegelow

Department of Paediatrics, Rigshospitalet, Copenhagen, Denmark, Department of Paediatrics, Queen Silvias Children’s Hospital, Gothenburg, Sweden, Department of Paediatrics, University of Tampere, Finland, Department of Paediatrics, University Hospitals, Astrid Lindgrens Barnsjukhus, Stockholm, Sweden, Department of Paediatrics, University Hospital Linköping, Linköping, Sweden, Department of Paediatrics, Lund University Hospital, Lund, Sweden, Department of Paediatrics, Syddanmarks University Hospital, Odense, Denmark, Department of Paediatrics, University Hospital of Uppsala, Uppsala, Sweden, Department of Biostatistics, University of Copenhagen, and The Institute of Gynecology, Obstetrics and Paediatrics, The Faculty of Medicine, University of Copenhagen, Copenhagen, Denmark

Summary

This study explored the feasibility and toxicity of individualized toxicity-titrated 6-mercaptopurine (6MP) dose increments during post-remission treatment with High-dose methotrexate (HDM) (5000 mg/m², ×3) in 38 patients with Childhood (ALL). Patients were increased in steps of 25 mg 6MP/m² per day if they did not develop myelotoxicity within 2 weeks after HDM. 6MP could be increased in 31 patients (81%). Toxicity was acceptable and did not differ significantly between groups. Patients receiving 75 mg/m² per day had significantly shorter duration of treatment interruptions of 6MP than the remaining patients (P = 0.03). This study shows individualized toxicity-titrated 6MP dosing during consolidation is feasible without increased risk of toxicity.

Keywords: acute lymphoblastic leukaemia, chemotherapy, children, consolidation, purine analogues.

Acute lymphoblastic leukaemia (ALL) protocols offer the same amount of chemotherapy per m², regardless of differences in drug disposition or susceptibility to side effects, except for maintenance therapy. Few childhood ALL studies have actually tested and confirmed that individual titration of therapy improves the cure rate (Evans et al., 1998; Schmiegelow et al., 2003). 6-mercaptopurine (6MP) is an essential drug in childhood ALL and is often given with High-Dose Methotrexate (HDM) and 6MP dosage determines the risk of post-HDM toxicity (Nygaard & Schmiegelow, 2003; van Kooten Niekerk et al., 2008).

A previous study of response to a combination of HDM with 6MP demonstrated that patients heterozygous for TPMT had a significantly lower rate of minimal residual disease
positivity at the end of a consolidation therapy containing 6MP/HDM compared with patients with two wild-type alleles (Stanulla et al, 2005). We expect that a similar effect could be obtained with 6MP dose increments.

The purpose of this pilot study was to test the feasibility of an individual, toxicity-titrated 6MP increment strategy during consolidation in post-remission treatment of lower risk childhood ALL.

Methods
The Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL 2008 Pilot study was a non-randomized, multicentre, uncontrolled trial. The study was approved by the National Medicines Agencies (EudraCT no: 2007-004021-19) and the National Ethical committees (H-A-2007-0067) and is registered at clinicaltrials.gov (ID NCT00548431).

Patients
Thirty eight patients (aged 1–0–17-9 years) with non-high risk ALL were included at eight centres in Denmark, Finland and Sweden at the start of their post-induction treatment. Non-high risk patients were defined as B-cell precursor ALL (BCP) with white blood cell count at diagnosis <100 x 10⁹/l. Patients with TPMT deficiency and high-risk cytogenetics were excluded. Patients were in remission at day 29 after a 4-week, 2 month consolidation phase, immediately post induction. 6-mercaptopurine increments were tested within the frame of a 2 month consolidation phase, immediately post induction (Fig 1).

6MP increments
Oral 6MP was initiated day 30 (25 mg/m² per day). 6MP was not experience an absolute neutrophil count (ANC) <0.5 x 10⁹/l and/or a platelet count <50 x 10⁹/l within 2 weeks after the start of the first HDM (day 36), the dose of 6MP was increased at Timepoint 1 (TP1 = day 51) to 50 mg/m². If the patient did not experience an ANC <0.5 x 10⁹/l and/or platelet count <50 x 10⁹/l within 2 weeks after the start of the second HDM (day 57), the dose of 6MP was increased by 25 mg/m² per day at TP2 (day 72) to either 50 or 75 mg/m² per day. 6-mercaptopurine treatment was interrupted if the ANC fell below 0.5 x 10⁹/l and/or the platelet count was <20 x 10⁹/l and/or the serum-aminotransferases increased above 20 x upper normal limits (UNL) and/or the bilirubin rose above 2 x UNL and/or the International Normalized Ratio (INR) rose above 1.5. Irrespective of the reason for intermitent treatment interruptions, oral 6MP therapy was given at a minimum dose of 25 mg/m² per day from the start of each HDM course and 7 d onward.

If the patient experienced an ANC <0.5 x 10⁹/l and/or a platelet count <50 x 10⁹/l following the second HDM, 6MP therapy was interrupted and not restarted until the ANC and platelet count had risen to at least 0.5 x 10⁹/l and 50 x 10⁹/l, respectively. 6MP was restarted at 25 mg/m² per day. 6MP was given once daily in the evening. In addition to documenting the actual 6MP dose given, methylated metabolites of 6MP (E-MeMP) were measured throughout treatment to monitor treatment compliance (Table I).

Toxicity
Toxicity was recorded throughout the study in a Case Report Form (CRF). Adverse Events were scored according to the National Cancer Institute Common Toxicity Criteria (CTC) guidelines version 2.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf). The parents and/or patients recorded side effects and symptoms in the patient diary.

TPMT analysis
All patients had their TPMT genotype and phenotype determined at the time of diagnosis. Genotyping and phenotyping was performed as previously described (Otterness et al, 1997; Schmiegelow et al, 2003, 2009a).

Measurements of study drug metabolites
E-MeMP was measured throughout the study as previously described (Kamen et al, 1976; Bruunshuus & Schmiegelow, 1989).
Short Report

Table I. Median number of days with 6MP treatment interruptions during consolidation. E-MeMP at day 85, adjusted for day 50 E-MeMP.

<table>
<thead>
<tr>
<th>Group</th>
<th>Median days of interruption (accumulated number of days with interrupted 6MP treatment from days 30 to 85) (Min; Max)</th>
<th>Measure of compliance (E-MeMP) Adjusted Relative Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1yesTP2yes (N = 13)</td>
<td>0 (0; 17)----------------------------------------------------------------------------------------------------------</td>
<td>5.89 (3.42; 10.12)</td>
</tr>
<tr>
<td>TP1yesTP2no (N = 5)</td>
<td>0 (0; 4)------------------------------------------------------------------------------------------------------------</td>
<td>5.41 (2.44; 12.02)</td>
</tr>
<tr>
<td>TP1noTP2yes (N = 8)</td>
<td>1 (0; 11)-----------------------------------------------------------------------------------------------------------</td>
<td>1.17 (0.62; 2.24)</td>
</tr>
<tr>
<td>TP1noTP2no (N = 12)</td>
<td>7.5 (0; 22)----------------------------------------------------------------------------------------------------------</td>
<td>1.63 (0.95; 2.78)</td>
</tr>
</tbody>
</table>

E-MeMP, Erythrocyte level of Methylated 6-Mercaptopurine metabolites; TP1noTP2no: No 6MP increments. TP1yesTP2no: Increment at first time point, but not at second time point. TP1noTP2yes: Increment at second time point but not at first time point. TP1yesTP2yes: Increments at both time points.

Statistics

Exact binomial tests were used when comparing the proportion of patients able to tolerate an increased dose to the target proportion of 40% (30% + 10%). Confidence intervals (95% CI) for proportions were calculated using exact methods. For comparing the four groups in terms of “days of 6MP discontinuation during consolidation treatment”, and of toxicity, an exact, non-parametric test was used. For testing E-MeMP at day 85 as compared to the level at day 50, the log transformed red blood cell metabolite levels were used and we compared the adjusted relative means at day 85 for the four groups, adjusting for day 50 levels. The most common adverse events were fever, pain and mucositis. The occurrence did not differ significantly between the four groups. Liver toxicity (elevated Aminotransferases) was common in all four groups, but did not differ significantly.

Two cases of pancreatitis were recorded. One (CTC grade IV pancreatitis) at the end of consolidation (day 84 in group TP1yesTP2yes), and one grade III-IV pancreatitis, 4 weeks after the start of consolidation treatment (group TP1noTP2yes).

Metabolite measurements

All four groups had increasing levels of MeMP from TP1 to TP2, and to the last day of 6MP treatment (day 85) (Table I). The groups TP1noTP2yes and TP1yesTP2yes both increased 6MP dose at TP2 (during the third HDM) and had significantly higher levels of E-MeMP compared to groups TP1yesTP2no and TP1noTP2no. The four groups were statistically significantly different with respect to day 85 E-MeMP adjusted for day 50 E-MeMP (P = 0.0004).

This pattern of E-MeMP measurements confirms good adherence to the documented 6MP treatment.

Discussion

Several studies have shown large inter individual variations in drug disposition, leading to significant inter individual differences in systemic and cellular exposures to the unmetabolized maternal drugs or cytotoxic metabolites (Schmiegelow & Ifversen, 1996; Evans et al., 1998; Schmiegelow et al., 2003; Stanulla et al., 2005; Avramis & Spence, 2007; Davidsen et al., 2008), influencing both the risk of relapse and toxicity.
The combination of low dose 6MP in combination with HDM has been used in Berlin-Frankfurt-Münster, NOPHO and other protocols for several decades. However, this study is the first to incorporate individualized 6MP dosage into a HDM-containing consolidation therapy.

The present study indicates that only one-third of patients are at the maximum tolerated toxicity on the standard 6MP consolidation treatment of 25 mg/m² per day. Importantly, patients receiving increased 6MP doses did not experience interruption, the toxicity in the group treated with the highest measured as cumulative number of days with 6MP treatment during consolidation.

Toxicity was lowest in the group increasing 6MP at both time points. Patients qualified for 6MP increments in the absence of significant myelotoxicity. In particular, when measured as cumulative number of days with 6MP treatment interruption, the toxicity in the group treated with the highest doses of 6MP was significantly less than for the other groups.

Despite expected adverse events, the present consolidation treatment was well tolerated. In conclusion, the present study showed individualized, toxicity-titrated 6MP increments during consolidation is feasible, without risk of severe toxicities. The study did not, however, address the event-free survival or overall survival for the groups that increased 6MP treatment versus the group with no 6MP increments. In the ongoing NOPHO ALL 2008 protocol, this issue is being explored in a randomized design.

Acknowledgements

All authors participated in performing the research. Thomas Leth Frandsen and Kjeld Schmiegelow designed the research study, analysed the data and wrote the paper.

Conflicts of interest

The authors have no personal or financial conflicts of interest related to the preparation and publication of this article.

References


