LETTER TO THE EDITOR

Cerebral Sinovenous Thrombosis in Children and Young Adults with Acute Lymphoblastic Leukaemia- a Cohort study from the United Kingdom

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Cerebral sinovenous thrombosis (CSVT) complicates therapy in 1-2% of children and young adults with acute lymphoblastic leukaemia (ALL) (Qureshi et al. 2010; Ranta et al. 2015; Caruso et al. 2006). In childhood, it has a mortality of 8-13% and can cause long-term neurological morbidity (deVeber et al. 2001; Ranta et al. 2015; Wasay et al. 2008) In addition, ALL therapy may be compromised by a reluctance to interrupt anticoagulation for intrathecal treatment and delayed/missed doses of L-asparaginase due to concern about thrombus progression or recurrence (Silverman et al. 2001).

The aim of this retrospective study was to identify individuals who developed CSVT during ALL therapy on the Medical Research Council (MRC) UKALL 2003 trial (http://www.isrctn.com/ISRCTN07355119) and to characterise their thrombotic risk factors, presenting features, management and outcome.

Between 2003 and 2011, 45 UK centres participated in the trial, which recruited children and young adults aged 1- 24 years. This was a randomised study to investigate use of minimal residual disease (MRD) monitoring to guide the intensity of ALL therapy (Vora et al. 2014; Vora et al. 2013). Pegylated (PEG) asparaginase (Oncaspar®; MEDAC GmBH, Germany) 1000 units/m^2 intra-muscularly was administered twice during the induction phase. All participants received oral dexamethasone 6mg/m^2/day throughout induction, interim maintenance and maintenance phases.

CSVT cases were identified by screening adverse event reports for central nervous system (CNS) thrombosis and grade III/IV serious adverse events in the

coagulation/thrombosis category. Reporting forms were sent to individual centres for collection of additional data. Ethical requirements were covered by overall consent for trial participation. Individuals with CSVT were compared to the remaining trial population, who did not have CSVT, using information from the study database. Statistical significance was measured for categorical variables using the Pearson chi-squared test. The overall effect of all variables was assessed using binary logistic regression.

Amongst 3126 trial participants, 46 cases of CSVT were identified. Information was returned for 45 cases, 2 of which were excluded as arterial events. 43 cases of CSVT were included in the final analysis, giving an incidence of 1.4%.

Table I compares the demographic features and disease characteristics between individuals who developed CSVT and those who did not. The CSVT cohort was significantly older, and were more likely to have high-risk cytogenetics but this effect was not independent of age. 33/43 (77%) of CSVT occurred during induction therapy. Median time from leukaemia diagnosis to thrombosis was 29 days (IQR: 22-35). All cases had received L-asparaginase prior to CSVT and 32/43 (74%) had received 2 doses. 77% of cases occurred within 3 weeks of the second dose of L-asparaginase (**Fig. 1**).

All cases were symptomatic. Frequent presenting features were neurological impairment (65%), seizures (56%) and headaches (47%). Concurrent intracranial haemorrhage (ICH) was present in 13 cases and cerebral infarction in 5.

Additional risk factors for thrombosis included hospital stay (22 cases), immobility for > 3 days (5), infection (5), dehydration (3) and use of an oestrogen-containing oral contraceptive pill (2). 17 cases (40%) had no additional risk factor. A thrombophilia screen was performed in 11 cases (26%) and was normal in 8. Two had a reduced Protein S level and 1 was heterozygous for the Factor V Leiden (F506Q) mutation. 21 individuals had an anti-thrombin (AT) level measured, of which 10 were below the reference range. Of the 10 cases that occurred post induction, 8 were hospital in-patients at the time of presentation and 5 had > 1 additional risk factors.

Anticoagulant therapy was administered to 39/43 (91%). Three did not receive anticoagulation due to the presence of ICH. The majority who were treated received low molecular heparin (LMWH) (97%). AT concentrate was administered to 2 and fresh frozen plasma to 1. Median duration of anticoagulant therapy was 3 months (IQR 3-6 months).

ALL therapy was modified due to CSVT in 25 cases (58%). Systemic chemotherapy was delayed in 10 and doses missed in 4. Intrathecal chemotherapy was delayed in 6 and doses missed in 2. Of 42 cases who were scheduled to receive further doses of L-asparaginase, 16 (37%) received no further doses. An additional 2 missed doses but had L-asparaginase re-introduced later. Of those re-exposed, the majority (22/26) received LMWH thromboprophylaxis during re-exposure.

Four individuals with CSVT died, one due to their thrombotic event (in association with extensive ICH). Neurological morbidity was reported in 5 cases (12%) at a

median of 41 months follow up, 4 of whom had ICH at presentation. There were no recurrent thrombotic events.

Survival of the CSVT cohort at the end of the trial period (median follow up of 70 months) was 39/43 (91%), comparable to 93% survival for the total trial population. Relapse rate did not differ between those with CSVT and those without, 91% vs. 87%, respectively (p=0.473), at the end of the trial period (Vora et al. 2013).

Ranta *et al*. recently published a cohort of 20 children who presented with CSVT during ALL treatment with the Nordic Society of Paediatric Haematology and Oncology (NOPHO) 2008 protocol, an incidence of 1.9% (20/1038). Association with L-asparaginase (80% of cases occurring within 2 weeks of L-asparaginase), steroid, co-administration of L-asparaginase and steroid, and early stages of treatment (< 5 months) was noted (Ranta et al. 2015). In the NOPHO 2008 protocol L-asparaginase was commenced post-induction meaning that CSVT presented later after diagnosis than in the UK cohort. Ranta *et al.* did not identify an association with age, although this was not true for all thrombotic events on the NOPHO protocol, where the adjusted hazard ratio for individuals aged 15-17 years was 4.0 (Tuckuviene et al. 2016). In contrast to the UK cohort, the NOPHO cohort had a higher thrombosis-related mortality rate with 2 deaths (10%) although the cohort was small. ALL treatment was altered in 12/18 with no recurrent thrombosis despite further exposure to L-asparaginase in a proportion of the cohort (Ranta et al. 2015).

CSVT occurring during treatment of ALL in children and young people is associated with a small risk of mortality and neurological morbidity, along with

interruption/alteration of leukaemia therapy, but no identifiable impact on relapse of leukaemia or survival. Re-exposure to L-asparaginase with LMWH thromboprophylaxis is possible without risk of recurrence. Older age is a risk factor for CSVT. The benefit of thromboprophylaxis, either using LMWH or AT concentrate, during ALL therapy in childhood has not been confirmed (Mitchell et al. 2003; Mitchell et al. 2010). There is an ongoing trial to investigate the use of prophylactic Apixaban in children with recently diagnosed ALL and a CVL (Bristol-Myers Squibb, https://clinicaltrials.gov/ct2/show/NCT02369653).

The temporal relationship of CSVT to L-asparaginase administration during ALL therapy would support studies to evaluate the use of thromboprophylaxis during this period of increased risk.

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