Hyperferritinaemia in paediatric ALL: what does it mean?

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As long-term survival of paediatric ALL improves, emphasis on the recognition and treatment of late effects of therapy is increasing. Iron overload is a known cause of morbidity in chronically transfused patients, results from as few as 10 transfusions and has an overlapping toxicity profile with chemotherapy(Eng and Fish 2011).

We sought to assess red blood cell (RBC) transfusion requirements and evaluate ferritin levels and bone marrow aspirate (BMA) staining in the assessment of iron status in paediatric ALL. 28 consecutive children treated for ALL between August 2010 and January 2014 at the Royal Hospital for Sick Children, Edinburgh were included for analysis. RBCs were administered if the haemoglobin level fell to less than 80 g/L at a standard paediatric dose of 15ml/kg. Serum ferritin was measured 3-monthly up to 1 year, then 6-monthly up to 3 years. BMA iron was assessed by Perl's Prussian blue, where BM haemosiderin deposition is graded from 0 (no stainable iron) to 6 (very heavy), normal range is 1-3 (Hughes*, et al* 2004).

Patient characteristics are summarised in Table I. All patients required RBCs, with a median of 195ml/kg (range 45-570) of packed RBCs per child, corresponding to 13 units and a median iron burden of 130mg/kg (range 30-380). RBC requirements were significantly higher in children with high risk disease compared to standard risk (281 ml/kg versus 150ml/kg, p=0.01). RBC transfusion volumes were non-normally distributed, with 25% requiring 10 units and outliers receiving up to 50 transfusions.

Median ferritin at diagnosis was 629 µg/L (range 76-2790) and end-of-treatment ferritin values normalised in only 1 patient. A ferritin value >500 µg/L was recorded in 93% (26/28) during the course of treatment. 11% of patients had a ferritin >10,000 µg/L recorded. Ferritin was significantly higher in the high-risk than standard-risk cohort (median 2089 µg/L versus 698 µg/L, p=0.006). There was no significant correlation between serum ferritin and BMA iron staining.

At day 28, median BMA iron stain was 3 (n=13, range 0-4). 14 day 28 BMAs (52% of total) were aparticulate, preventing iron storage assessment. Twenty BMAs were available from patients at a later stage of treatment; 4 (20%) were aparticulate and median iron grade was 4 (range 2-5). 35% of BMAs assessed at a later stage of treatment demonstrated ≥4+ iron staining, consistent with iron overload. There was a significant correlation between iron transfused (mg/kg) and BMA grading. (r=0.7 p=0.035)

Our findings indicate that patients with paediatric ALL receive a significant iron burden during therapy, placing them at risk of later morbidity and thatserum ferritin is not a reliable indicator of iron status in this population. Hyperferritinaemia has a wide differential aside from iron overload, including infection, inflammation, and haemophagocytic lymphohistiocytosis (HLH) (Lehmberg, *et al*, 2015). Extreme hyperferritinaemia in the context of ALL is not specific for a diagnosis of HLH although ALL is a recognised cause of secondary HLH.

As the focus in paediatric ALL shifts from survival to preventing long-term morbidity, the need to establish clear guidelines for screening and management of iron overload in the context of paediatric ALL is evident.

Table I

Patient characteristics

Median age (range) at diagnosis (years)	3.5 (4 weeks - 15 years)
Sex	
Male	17 (61%)
Female	11 (39%)
Primary diagnosis	
B cell ALL (standard risk)	12 (43%)
B cell ALL (high risk)	10 (36%)
T cell ALL	3 (11%)
Infant ALL	3 (11%)
Treatment protocol	
UKALL 2011	12 (43%)
UKALL 2003	10 (36%)
Interim guidelines	3 (11%)
Interfant 06	3 (11%)
Median haemoglobin at diagnosis (g/L)	79 (32-109)

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