Earlier initiation of transfusional and iron chelation therapies in recently born children with transfusion-dependent thalassemia

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To the Editor

Current guidelines for thalassemic patients recommend to initiate transfusion after a confirmed diagnosis and with a hemoglobin level <7 g/dL or, irrespective of hemoglobin, with any of the following manifestations: poor growth, fractures, facial changes, and any other sign of clinically significant extramedullary haematopoiesis [1].

In this study, we evaluated age and hemoglobin value at the first transfusion in 300 children with homozygous thalassemia (164 males, 136 females) born between 1966 and 2016 and under regular observation and treatment at the Ospedale Microcitemico “A.Cao”, Cagliari (Italy).

We also assessed if these two variables have had an impact on the time of initiation of iron chelation therapy.

In our cohort, 66 children (22.0%) were born with a prenatal diagnosis and 57 (19.0%) were diagnosed with homozygous beta thalassemia at birth, while 177 (59.0%) were diagnosed after the occurrence of signs and symptoms of anemia. The haemoglobin value at the first transfusion was available for 237 children, and the date on which iron chelation began was available for 271 children.

The age at the first transfusion was not different between patients with a preclinical diagnosis (prenatal or at birth) and patients diagnosed based on the appearance of symptoms (12.7 ± 16.2 months vs. 15.1 ± 15.6 months, n=66 and 177, respectively, p=0.2).

The percentages of children who started transfusion before 6 months of age and after 24 months were also similar in these two groups (42% and 37% and 13% and 19%, respectively p=0.37 and 0.15).

However, hemoglobin values at the first transfusion were significantly higher in patients with prenatal diagnosis or diagnosis at birth vs. those diagnosed based on symptoms [7.5 ± 0.9 g/dL (range 5 – 10) and 6.5 ± 1.1 g/dL (range 3 – 8.5) in cases of a diagnosis at symptoms appearance (p<0.0001)].

The year of birth showed a strong correlation with both the mean age at first transfusion (lower in more recent births) and the mean hemoglobin at the first transfusion (higher in more recent births, p=0.004 and p<0.0001, respectively). Compared across 4 birth cohorts, each spanning 10 years, hemoglobin values at the first transfusion showed that the proportion of children with hemoglobin below 7 g/dL progressively decreased (p<0.0001) (Figure 1). Among the 68 patients born after 2005, transfusion therapy was initiated in 53 patients (77.9%) with a hemoglobin value ≥7 g/dL and in 26 patients (38.2%) with a
hemoglobin value ≥8 g/dL. Only 22.1% of children started transfusion simply on the basis of the laboratory criterion over the last decade, while the remainder started on the basis of the clinical criteria.

Current guidelines for iron chelation therapy recommend that therapy should not be started until serum ferritin levels reach 1000 μg/L and only after the first 10-20 transfusions [1]. We wondered if the observed decrease in the age at the first transfusion was associated with changes in the initiation of chelation therapy and particularly if changes could be seen for patients below 2 years of age, since limited data are available on the use of deferiprone in children and deferasirox is not indicated at this young age.

Deferasirox was approved in the European Union on August 28, 2006: of the 53 children born after that date and currently on iron chelation, 32 (60.4%) started chelation therapy before 24 months of age (at a mean age of 17.9 ± 3.6 months). Iron chelators other than desferrioxamine were used in 4 children as part of a clinical trial while 28 received subcutaneous desferrioxamine.

Our findings indicate therefore a change in the therapeutic approaches to thalassemia with earlier initiation of transfusional therapies making earlier chelation necessary.

We can speculate that these changes may be a consequence of:

- A greater awareness of the fact that the diagnosis of non-transfusion-dependent thalassemia carries higher morbidity than previously recognized and, conversely, an ameliorated prognosis of thalassemia major, which makes the decision to start transfusion easier [2];
- A higher risk of alloimmunisation for patients first transfused at an older age [3];
- A lower threshold to treat or prevent skeletal deformities both for cosmetic reasons, as well as being an indication of a future exhaustion of the compensatory mechanism for the severe anaemia [4];

New findings on the benefits of early chelation to prevent some of the iron related complications, such as hypogonadism together with new parameters for predicting the appearance of toxic free iron and the need to start iron chelation [5-6].

In conclusion, our results show a progressive decrease in age together with an increase in hemoglobin values at the first transfusion for children with thalassemia. This trend is accompanied by an anticipation of the starting age of iron chelation, even before the age of two, when desferrioxamine alone is indicated and has been widely tested. If this trend is
confirmed in other centers and studies, attention should be paid to the need of specific studies on the safety and efficacy of the new oral chelators for these younger ages.

**Authorship**

Contribution: RO designed the research study, analyzed the data and wrote the paper. AZ and FT gave a substantial contribute to the acquisition of data. FA, GBL, MM, VO, MPP, MP, MRC, CD, PM, MRD, ARD and SB contributed to acquire, analyze and interpreter the data. All the Authors revised the paper critically and approved the final version.

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**References**

Figure 1. Haemoglobin level at the first transfusion in 237 children with thalassaemia major according to cohorts of birth.

297x209mm (300 x 300 DPI)