The era of comparable life expectancy between thalassaemia major and intermedia: Is it time to revisit the major-intermedia dichotomy?

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Summary

In the last few decades, the life expectancy of regularly transfused β-thalassaemia major (TM) patients has dramatically improved following the introduction of safe transfusion practices, iron chelation therapy, aggressive treatment of infections and improved management of cardiac complications. How such changes, especially those attributed to the introduction of iron chelation therapy, improved the survival of TM patients to approach those with β-thalassaemia intermedia (TI) remains unknown. Three hundred and seventy-nine patients with TM (n = 284, dead 40) and TI (n = 95, dead 13) were followed retrospectively since birth until 30 June 2015 or death. Kaplan-Meier curves showed statistically significant differences in TM and TI survival (P < 0.0001) before the introduction of iron chelation in 1965, which were no longer apparent after that date (P = 0.086), reducing the Hazard Ratio of death in TM compared to TI from 6.8 [95% confidence interval (CI) 2.6–17.5] before 1965 to 2.8 (95% CI 0.8–9.2). These findings suggest that, in the era of iron chelation therapy and improved survival for TM, the major-intermedia dichotomy needs to be revisited alongside future directions in general management and prevention for both conditions.

Keywords: survival, thalassaemia, classification, severity.
An estimated 300,000 children are born each year with a genetic defect of one or more genes that encode α- or β-globin chains (Weatherall, 2011). The presentation and clinical course of β-thalassaemia syndromes varies greatly and depends on the underlying combination of genetic anomalies (Galanolou, 2012; Thein, 2013). Patients with the severe form of β-thalassaemia, such as β-thalassaemia major (TM), present early in infancy with debilitating anaemia that requires life-long regular transfusions for survival. However, patients with milder forms of thalassaemia, such as β-thalassaemia intermedia (TI), present later in life with a less severe anaemia and remain transfusion-independent except within specific and temporary clinical settings (Modell & Berdoukas, 1984; Cunningham et al, 2004). Such designations of severity based on presenting anaemia and transfusion requirement have traditionally implied a corresponding clinical course severity. Thus, although transfusions ameliorate the anaemia in TM, the disease picture still implies great morbidity and mortality primarily due to transfusional iron overload.

Nevertheless, the survival of TM patients has greatly improved over the last few decades as illustrated by large registries and observational cohorts (Brittenham et al, 1994; Calleja et al, 1998; Borgna-Pignatti et al, 2004a; Cunningham et al, 2004; Roudbari et al, 2008; Maggio et al, 2009a; Telfer, 2009; Marsella et al, 2010; Ladis et al, 2011; Kwiatkowski et al, 2012; Rajaeefard et al, 2015; Tubman et al, 2015; Zamani et al, 2015). Cunningham et al (2004), on behalf of the Thalassaemia Clinical Research Network (TCRN), reported such improvements and associated them with the dramatic advances in management of TM patients over the past 40 years. Borgna-Pignatti et al (2004a) also reported data from a 30-year long Italian cooperative study including over 1000 thalassaemia patients born since 1960, and showed better survival rates for patients in younger birth cohorts (P < 0.01) and in females (P = 0.0003). More recently, Ladis et al (2011) showed that the standardised mortality ratio (standardised for sex and ages 20–40 years) for 1044 Greek TM patients improved significantly as compared to the general population, declining from 28.9 in 1990–1999 to 13.5 in 2000–2008. Such improvements are commonly attributed to several factors, including the introduction of iron chelation therapy, screening for blood-borne viruses, aggressive treatment of infections, and improved treatment of cardiac complications.

Despite these observations, the question of how these advances in management altered the disease clinical burden and life expectancy of TM patients compared to TI remains unknown. More specifically, the effects of introducing iron chelation therapy to manage the primary pathogenic factor, transfusional siderosis, on narrowing the gap in severity between the major and intermediate forms of thalassaemia have not been formally evaluated. The answer to such question is of high merit, as it carries implications on public health awareness, treatment and prevention strategies for the thalassaemias. With this background, this study aimed to compare survival of TM and TI patients in a large cohort from Italy, and analyse factors contributing to the observed differences, particularly with regard to the introduction of iron chelation therapy. Our study analysed only beta-thalassaemia intermedia and did not include other forms of non-transfusion dependent thalassaemia (NTDT) such as HbH disease and HbE/thalassaemia, therefore we specifically utilize the term TI and not the term NTDT, which includes other forms of disease.

Materials and methods

The study was based on data retrospectively retrieved from several randomized clinical trials conducted by the Campus of Haematology Franco and Piera Cutino – A.O.O.R. Villa Sofia-V Cervello, Palermo in Italy. Patients were diagnosed with TM or TI according to international recommendations (Modell & Berdoukas, 1984; Cunningham et al, 2004). Patients with a haemoglobin level at presentation of <70 g/l and age of onset <2 years were considered to have TM, while patients with a haemoglobin level at presentation of ≥70 g/l and an age of onset ≥2 years were considered to have TI (Modell & Berdoukas, 1984; Cunningham et al, 2004). The diagnosis in both cases was confirmed by molecular studies as described elsewhere (Kutlar, 2007).

The oldest patient enrolled in this study was affected by TI and was born in 1935. Patients were followed from birth until 30 June 2015 or death. Retrieved data included demographics, clinical history for risk factors affecting survival [splenectomy, heart failure, arrhythmia, cirrhosis, diabetes, hepatitis C virus (HCV) infection confirmed by HCV-RNA]. The cause of death was also recorded for each deceased patient.

All patients were from an Italian background and were uniformly treated. TM patients received regular transfusions to maintain a haemoglobin level of 90–95 g/l. Splenectomy was performed if transfusional requirement exceeded 250 ml/kg/year. Standard iron chelation therapy in TM and TI patients (as indicated) was deferoxamine (DFO) as a subcutaneous infusion at a dose of 40–50 mg/kg/day from when it became available in 1965 until 1994. One hundred and forty-four patients with TM (from September 1994) and 48 patients with TI (from January 2001) started/switched to deferiprone (DFP) treatment (Maggio et al, 2002) in the context of randomized multicentre clinical trials (Maggio et al, 2002, 2009b; Calvaruso et al, 2015). Combination treatment with DFO and DFP was used from 1998 in TM patients with severe iron overload (Wonke et al, 1998), especially after reports of its effectiveness in controlling cardiac iron overload (Modell et al, 2008; Ambati et al, 2013). Deferasirox at starting doses of 20 mg/kg/day with appropriate dose escalation was introduced in 2006 for TM patients after its effectiveness as monotherapy or in association with DFO was established (Cappellini et al, 2006; Aydinok et al, 2015; Cassinerio et al, 2015).
Statistical analysis

Descriptive analyses were described as means ± standard deviations or errors, medians, or percentages. To compare survival curves in TM versus TI patients, Kaplan-Meier curves were constructed and the log-rank test (Collett, 2014) was conducted while stratifying data for the periods before and after the introduction of iron chelation therapy with DFO in 1965. Cox regression analysis (Collett, 2014) was also used to calculate hazard ratios (HR). All *P*-values are two sided with the level of significance set at <0.05.

Results

A flow chart describing patients included in this analysis is shown in Fig 1. Three hundred and seventy-nine patients were evaluated including 284 with TM (49.6% females) and 95 with TI (48.4% females). Demographic and clinical characteristics of patients with TM and TI are summarized in Table I. The mean age of patients was 35 years in TM and 51 years in TI. There was a statistically significant difference between age at first transfusion (*P* < 0.01) and total blood transfusion requirement (*P* < 0.01) between TM and TI patients, further confirming the validity of the diagnoses (Table I).

A total of 40 (14.1%) patients with TM and 13 (13.7%) patients with TI died. Among patients who died, 15% (*n* = 6) of TM and 76.9% (*n* = 10) of TI were born before the introduction of DFO in 1965 (Fig 1).

Clinical risk factors with the highest incidence in TM deaths were HCV-RNA positivity (55.0%) and cirrhosis (27.5%), while splenectomy (86.4%), HCV-RNA positivity (38.5%) and cirrhosis (38.5%) were the most common risk factors in TI deaths (Table I).

Table II summarizes the main causes of death. The most common cause of death in TM was heart damage (*n* = 16, 40%), followed by cancer (*n* = 3, 7.5%), liver cirrhosis (*n* = 3, 7.5%) and infections (*n* = 3, 7.5%). The most common causes of death in TI were cancer (*n* = 5, 38.5%), followed by infections (*n* = 3, 23.1%) and heart damage (*n* = 2, 15.4%) (Table II).

Kaplan–Meier curves of patients born before 1965 showed statistically significant difference in survival for TM versus TI (log-rank test, *P* < 0.001; Fig 2A). In contrast, survivals of
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Table I. Patients’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>TM Alive</th>
<th>TM Dead</th>
<th>Total</th>
<th>TI Alive</th>
<th>TI Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, mean ± SD</td>
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<tr>
<td>Age (years)</td>
<td>35.6 ± 7.4</td>
<td>30.6 ± 10.7</td>
<td>34.8 ± 8.1</td>
<td>50.4 ± 12.6</td>
<td>56.6 ± 14.1</td>
<td>51.2 ± 13.0</td>
</tr>
<tr>
<td>Age at first chelation (years)</td>
<td>3.3 ± 2.1</td>
<td>2.2 ± 1.9</td>
<td>3.3 ± 2.1</td>
<td>15.5 ± 14.4</td>
<td>25.4 ± 22.5</td>
<td>16.4 ± 15.3</td>
</tr>
<tr>
<td>Age at first transfusion (years)</td>
<td>2.2 ± 1.6</td>
<td>2 ± 1.9</td>
<td>2.1 ± 1.7</td>
<td>15.3 ± 14.7</td>
<td>31.4 ± 25.1</td>
<td>16.1 ± 15.4</td>
</tr>
<tr>
<td>Total blood transfusion (ml/kg/year), median (IQR)</td>
<td>8593 (2550)</td>
<td>9100 (1500)</td>
<td>8597 (2550)</td>
<td>3100 (5155)</td>
<td>2500 (4240)</td>
<td>3000 (4711)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>122 (50-0)</td>
<td>19 (47-5)</td>
<td>141 (49-6)</td>
<td>41 (50-0)</td>
<td>5 (38-5)</td>
<td>46 (48-4)</td>
</tr>
<tr>
<td>Male</td>
<td>122 (50-0)</td>
<td>21 (52-5)</td>
<td>143 (50-4)</td>
<td>41 (50-0)</td>
<td>8 (61-5)</td>
<td>49 (51-6)</td>
</tr>
<tr>
<td>Clinical history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Splenectomy</td>
<td>30 (12.3)</td>
<td>2 (5)</td>
<td>32 (11.3)</td>
<td>67 (81.7)</td>
<td>11 (84-6)</td>
<td>78 (82-1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (1.7)</td>
<td>13 (32.5)</td>
<td>17 (5.9)</td>
<td>1 (1.2)</td>
<td>1 (7.7)</td>
<td>2 (2-1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6 (2.5)</td>
<td>3 (7.5)</td>
<td>9 (3.2)</td>
<td>2 (2.4)</td>
<td>2 (15-4)</td>
<td>4 (4-2)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>7 (2.9)</td>
<td>11 (27.5)</td>
<td>18 (6.3)</td>
<td>5 (6-1)</td>
<td>5 (38-5)</td>
<td>10 (10-5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (4.1)</td>
<td>3 (7.5)</td>
<td>13 (4.5)</td>
<td>6 (7.3)</td>
<td>2 (15-4)</td>
<td>8 (8-4)</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td>62 (25-4)</td>
<td>22 (55)</td>
<td>84 (29-6)</td>
<td>12 (14-6)</td>
<td>5 (38-5)</td>
<td>17 (17-9)</td>
</tr>
</tbody>
</table>

Table II. Causes of death in TM and TI patients.

<table>
<thead>
<tr>
<th>Cause of death, n (%)</th>
<th>TM n = 40</th>
<th>TI n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>*3 (7-5)</td>
<td>*5 (38-5)</td>
</tr>
<tr>
<td>Heart damage</td>
<td>16 (40-0)</td>
<td>2 (15-4)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (7-5)</td>
<td>3 (23-1)</td>
</tr>
<tr>
<td>Multi organ failure</td>
<td>1 (2-5)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2-5)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>3 (7-5)</td>
<td>1 (7-7)</td>
</tr>
<tr>
<td>Other complications</td>
<td>2 (5-0)</td>
<td>1 (7-7)</td>
</tr>
<tr>
<td>related to thalassaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>11 (27-5)</td>
<td>1 (7-7)</td>
</tr>
</tbody>
</table>

TM, β-thalassaemia major; TI, β-thalassaemia intermedia. *2 deaths for hepatocellular carcinoma.

Discussion

Our findings indicate that life expectancy in TM became comparable to TI after the introduction of iron chelation therapy, decreasing the gap in mortality from a 6-8-fold increased risk to 2-8-fold. Improvement of TM survival during recent years has been consistently reported by different groups, including those from developing countries (Brittenham et al., 1994; Calleja et al., 1998; Borgna-Pignatti et al., 2004a; Cunningham et al., 2004; Roudbari et al., 2008; Maggio et al., 2009a; Telfer, 2009; Marsella et al., 2010; Ladis et al., 2011; Kwiatkowski et al., 2012, 2015; Tubman et al., 2015; Zamani et al., 2015). The survival in TM to TI has been compared in only one previous report by Rajaeefard et al. (2015), who showed an increased risk of mortality in TM over TI by only 1.54-fold (95% CI 0.94–2.53) in a cohort of Iranian patients followed in the Shiraz province. Our data echo these findings and further confirm this observation in Western cohorts. It also indicates that this observation is a relatively ‘recent’ phenomenon associated with the introduction of iron chelation therapy to manage transfusional siderosis.

Although survival in both patients groups has become comparable, the causes of mortality remain different. Heart damage was the leading cause of death in TM while cancer tops the list in TI and is potentially attributed to hepatocellular carcinoma. These differences may be attributed to varying iron chelation and HCV management practices spanning the cohort, which have considerably advanced since 1990 (Borgna-Pignatti et al., 2004a; Maggio et al., 2009a; Brittenham et al., 1994; Calleja et al., 1998; Cunningham et al., 2004; Ladis et al., 2011; Kwiatkowski et al., 2012, 2015; Zamani et al., 2015). The survival in TM to TI has been compared in only one previous report by Rajaeefard et al. (2015), who showed an increased risk of mortality in TM over TI by only 1.54-fold (95% CI 0.94–2.53) in a cohort of Iranian patients followed in the Shiraz province. Our data echo these findings and further confirm this observation in Western cohorts. It also indicates that this observation is a relatively ‘recent’ phenomenon associated with the introduction of iron chelation therapy to manage transfusional siderosis.

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Nonetheless, advances in improved survival in TM patients seem to be associated with a decline in cardiac deaths and increase in the incidence of hepatic disease (Borgna-Pignatti et al., 2004b, 2014; Cappellini et al., 2006; Mancuso et al., 2006; Modell et al., 2008; Pennell et al., 2011). Thus, similar studies in the future may reveal a different distribution of causes of death in TM patients.

The high rate of death from infection in TI (23%) may be related to the higher rate of splenectomy in TI patients (86-4%). These findings, associated with the risk of hypercoagulable state (Cappellini et al., 2012) and the lack of high quality evidence data for splenectomy in TM and TI (Easow Mathew et al., 2016), suggest that the recommendation of this procedure should be reconsidered. Our findings not only illustrate improved survival in TM patients, but also indicate lack of such improvement in TI.

Awareness of the disease burden in TI, more recently categorized as non-transfusion-dependent thalassemia (NTDT) (Musallam et al., 2012) is only recently starting to emerge, with reports showing multiplicity of clinical complications, such as endocrinopathy, bone disease, thromboembolism, pulmonary hypertension, cerebrovascular and neuronal damage, liver fibrosis or cirrhosis and increased risk of hepatocellular carcinoma – all potentially contributing to an increased risk of morbidity and mortality (Borgna-Pignatti et al., 2004b, 2010, 2014; Mancuso et al., 2006; Musallam et al., 2012; Taher & Cappellini, 2014). As TI has classically been regarded as a milder form of thalassemia, advances in management have been thus far limited. The role of regular transfusions in managing TI has recently been illustrated (Aessopos et al., 2007; Borgna-Pignatti et al., 2010; Taher et al., 2014). Moreover, management of iron overload attributed to increased intestinal absorption has probably lagged behind, especially with the recently uncovered potential of underestimation of iron burden when relying on serum ferritin measurements. Management guidelines for TI, in fact, have only recently become available (Aessopos et al., 2007; Borgna-Pignatti et al., 2010; Musallam et al., 2012; Taher & Cappellini, 2014). Collectively, these findings suggest that it is probably necessary to overcome the major-intermedia dichotomy and turn to clinical decisions for the management of TM and TI that are based on prognostic risk factors that could influence survival, rather than severity of disease at presentation. The similarity in expectancy between TM and TI in Western countries also suggest that strategies for prenatal diagnosis in TM must be reviewed.

In conclusion, our study suggests that advances in transfusion and iron chelation therapy today have extended the life expectancy of TM patients to come close to those with TI, thus changing the paradigm that these diseases come with different prognoses. This paradigm change, if confirmed by larger studies from other groups, deserves revision of future approaches in the management and prevention of both disease forms.

Acknowledgements

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Authors’ contribution
A.V. assisted with statistical design, data analyses and statistical interpretation, and wrote the manuscript; A. M. designed research questions, assisted with medical interpretation, and wrote the manuscript; G. C. assisted with data collection; E. L., G.C., A. Q., C. G., L. C. R., L. P., L. C., F. G., A. F., V. C., C. A., S. C., M. R., L. P., C. F., M.F., R. DM contributed to patient enrolment and reviewed the manuscript for important intellectual content.

Conflict-of-interest disclosure
The authors declare no competing financial interests.

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