Disorders of Erythropoiesis

Risk factors for death in patients with β-thalassemia major: results of a case-control study

This retrospective one to one matched case-control study was aimed at evaluating risk factors for death in β-thalassemic patients followed in Italian centers between 1997 and 2001. The mortality risk was lower in patients with good compliance to iron chelation therapy and in those treated with deferiprone.

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The natural history of β-thalassemia major has changed radically over the last 30 years, following the introduction of iron chelation therapy combined with regular blood transfusions. Italian studies have clearly shown that mortality rates are decreasing, mainly as a consequence of better management of iron overload.[1,2]

Subcutaneous desferrioxamine (DFO) represents the current best practice in treating patients. However, poor compliance to treatment with DFO is a major problem, particularly among adolescents and young adults and limits the number of well-chelated patients.[3]

The introduction in 1999 of the oral chelator deferiprone, as second line treatment, ensured a better compliance thanks to its more convenient route of administration.[4] In addition deferiprone administration has also proven to be effective in removing myocardial iron and reversing cardiac damage.[5,6] In spite of this, disease and treatment-related complications progress over time in many patients, causing severe morbidity and shortening life expectancy even in patients with access to good medical treatment. The aim of our study was to evaluate risk factors for death in patients with thalassemia major.

A retrospective one to one matched case-control study was conducted, collecting data from 31 Italian Centers for the treatment of thalassemia in the period 1997-2001 (Table 1). The Scientific Review Board of the *Fondazione Italiana Leonardo Giambrone per la guarigione della thalassemia*, acting as the Institutional Review Board, approved the study. According to European Rules (Dir. 20/2001/EC), since this was a retrospective, non-interventional study not involving human experimental procedures, approval from an Independent Ethics Committee was not required. During the study period, a total of 42 patients died (27 males and 15 females). For each deceased patient (case), a control of the same sex and aged in the range of ± 4 years of the case's age was selected. When more than one control met the matching criteria, the control patient was chosen randomly.

The main long-term prognostic factors 2 were included in the risk assessment analysis for death. In particular we considered age at first chelation, compliance to chelation therapy, inclusion of deferiprone in the treatment plan, ferritin levels, and organ damage.

Descriptive statistics on the groups of deceased and control subjects were performed. Fisher's exact tests and unpaired *t* tests were used to compare the groups. A conditional logistic regression analysis was applied to evaluate the effects on mortality of all the considered risk factors. Ages at first transfusion and chelation were included in the model as continuous factors, while all the other variables were categorized dichotomously, the absence of the risk factor being the reference category. Odds ratios (OR) and 95% confidence intervals were estimated.

Table 1. List of Italian thalassemia centers participating in this study.

Centers

- Cl. Ped. Università, Bari (Dr. Del Vecchio)
- Cl. Ped. Spedali Civili, Brescia (Dr. Notarangelo)
- Osp.Nostra Signora Di Bonaria, S.G. Monreale (Dr. Baztella)
- A.O. Osp.Maggiore di Crema, Crema (Dr. Colombo)
- A.O. Ist. Ospedalieri di Cremona, Cremona (Dr. Bodini)
- P.O. Annunziata, A.O.Cosenza, Cosenza (Dr. Bisconte)
- Az. Osp. Garibaldi, Catania (Dr. Magnano)
- A.O. Pugliese Ciaccio, Catanzaro (Dr. Galati)
- Arcispedale S. Anna, Ferrara (Dr. De Sanctis)
- Casa della sofferenza IRCCS, San G. Rotondo (Dr. Violi)
- Osp. Lecco Alessandro Manzoni, Lecco (Dr. Invernizzi)
- Pres. Osp.San Leopoldo, Merate (Dr. Erba)
- Osp.Maggiore di Lodi, Lodi (Dr. Paolillo)
- A.O. Univiversitaria "G.Martino", Messina (Dr. Meo)
- Osp. Civile di Rho, Rho (Dr. Vismara/Ferriciotti)
- Osp. Di Magenta, Magenta (Dr. Pandolfi)
- Ist. Cl. di Perfezionamento, Milano (Dr. Carnelli/R.Ghilardi)
- Osp. Di Circolo di Melegnano, Zizzolo Predabisso (Dr. Rogari)
- Osp.Cardarelli, Napoli (Dr. Prossomariti)
- Osp.Cardarelli, Napoli (Dr. Filosa)
- Osp.Vincenzo Cervello, Palermo (Dr. Maggio)
- A.O. B.M.M, Reggio Calabria (Dr. D'Ascola)
- Osp. S.Eugenio, Roma (Dr. Cianciulli)
- Osp.Sandro Pertini, Roma (Dr. Santis)
- Osp. S.Maria della misericordia, Rovigo (Dr. Vaccari)
- A.O. Umberto I, Siracusa (Dr. Mangiagli)
- Cl. Ped. Univ.di Sassari, Sassari (Dr. Gallisai)
- Osp. SS Annunziata, Taranto (Dr. Stefàno)
- Osp. Mauriziano Umberto, Torino (Dr. Bertero)
- Osp.Busto Arsizio, Busto Arsizio (Dr. Somaschini)
- Osp. Iazzolino, Vibo Valentia (Dr. Di Giacomo)

The characteristics of the cases and controls are reported in Table 2. In the case group (deceased patients) the most frequent cause of death was cardiopathy (69%), followed by infections (14%), malignancy (5%), renal failure (5%), thrombosis (5%) and chronic liver disease (2%). Several clinical and therapeutic characteristics differed between the two groups. In detail, compliance to iron chelation therapy was judged good in 21% of deceased patients and in 67% of controls (p<0.001), while ferritin levels were high (mean value above 2000 ng/mL for the entire period) in more than 60% of cases and in 33% of controls (p=0.014). Moreover, controls were given deferiprone more frequently (38% vs 17%) and for a longer period (4.8 years vs 1.9 years, p=0.01) than were cases.

The results of the conditional logistic regression analysis, calculated as the OR, are reported in Table 3. Organ impairment was strongly associated with mortality. In particular the presence of cardiopathy increases the risk of death by 12.5 times and the presence of liver damage by 4.5 times; impairment of the endocrine system did not have any significant effect. In addition the presence of more than one organ impairment modified the expectancy of survival by increasing the risk of death 6.5 times. Other factors that increased the risk of death were serum ferritin levels over 2,000 ng/mL (for a 6-year period), which was associated with a 3.3 times increased risk, and delayed initiation of iron chelation therapy. Each year in which no treatment was administered increased the risk

Table 2. Characteristics of the cases and controls.

	Cases	*Controls*	*p value*
Age (years)	27.4±5.6 yrs (range 18-43)	29.7±5.7 yrs (range 19-41).	n.s.
Age at first transfusion (months)	14.1±12.3 (range 1-54)	20.2±17.4 (range 3-84)	0.06
Age at first chelation (years)	9.89±5.48 (range 2-24)	6.68±4.14 (range 1-21)	0.003
Treatment with deferiprone (n. pts, %)	7 (17%)	16 (38%)	0.03
Duration of therapy with DFO alone (years)	17.1±4.63 (range 7-34)	20.4±5.4 (range 2-29)	n.s.
Duration of therapy with deferiprone (years)	1.9±0.38 (range 0.4-4)	4.76±2.5 (range 1-9)	0.01
Good compliance (n/%)	9 (21%)	28 (67%)	<0.001
Six year-serum ferritin (n. pts, %) < 1000 ng/mL; 1000-2000 ng/mL; > 2000 ng/mL	6 (14%) 10 (24%) 26 (62%)	16 (38%) 12 (29%) 14 (33%)	0.014
Organ damage (n. pts%: heart; liver; endocrine system)	35 (83%) 36 (86%) 35 (83%), 0	12 (29%); 24 (57%) 31 (74%); 8 (19%)	<0.001 0.007 n.s. 0.005

Data are expressed as mean ± SD or as frequencies, according to the nature of the variables. ns: not significant.

Table 3. Association between death and risk factors (odds ratios and 95% confidence intervals).

Risk factors	*OR*	*95% I.C.*	*p*
Risk factors for death			
Heart impairment	12.5	4.36-35.79	<0.001
Liver impairment	4.5	1.56-12.97	0.005
Endocrine system impairment	1.77	0.61-5.14	n.s.
Serum ferritin > 2000 ng/mL	3.33	1.35-8.25	0.009
Age at first transfusion (years)	0.71	0.48–1.04	n.s.
Age at first chelation (years)	1.15	1.041–1.278	0.006
Protective risk factors			
Good compliance	7.33	2.76-19.48	<0.001
Treatment with deferiprone	3.08	1.11-8.56	0.03

ns: not significant.

(OR: 1.15). Contrariwise, the following factors were proven to have a protective effect on mortality: a) good compliance - patients with good compliance have a 7.33 times lower risk of incurring premature death than that of patients with a bad compliance; b) inclusion of deferiprone in the therapeutic plan (OR: 0.32, corresponding to a 3-fold reduction in the risk of death).

This multicenter study confirms that cardiopathy, poor compliance with chelation therapy and high ferritin levels contribute to the risk of death in patients with thalassemia major. It also suggests that including the oral chelator deferiprone in the therapeutic plan may protect against mortality. Anderson *et al.*[7] showed that conventional chelation treatment with subcutaneous DFO does not prevent excess cardiac iron deposition in two-thirds of patients with thalassemia major, placing these patients at risk of heart failure and its complications. A recent randomized, controlled trial of treatment with deferiprone or DFO showed that deferiprone monotherapy was significantly more effective than DFO over 1 year in improving asymptomatic myocardial siderosis.[8] In the light of our findings and of the available evidence, the combination of DFO and deferiprone[9,10] might represent the most appropriate therapeutic choice for many patients with β-thalassemia major.

Adriana Ceci, Paola Baiardi,* Mariana Catapano,* Mariagrazia Felisi,* Paolo Cianciulli,° Vincenzo De Sanctis,# Giovanni Carlo Del Vecchio,@ Carmelo Magnano,^ Anna Meo,§ Aurelio Maggio***

**Consorzio per le Valutazioni Biologiche e Farmacologiche, Pavia: °Ospedale "Sant'Eugenio", Roma; #Arcispedale S. Anna, Ferrara; @Policlinico Università, Bari; ^Ospedale "Garibaldi", Catania; §Policlinico Università, Messina: **Azienda Ospedaliera "V. Cervello", Palermo, Italy*

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Correspondence: Adriana Ceci, Consorzio per Valutazioni Biologiche e Farmacologiche, Via Palestro 26, 27100 Pavia, Italy. Phone: international +39.0382.25075. Fax: international +39.0382.536544. E-mail: aceci@cvbf.net

References

1. Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, et al. Survival and causes of death in thalassaemia major. Lancet 1989;2:27-30.
2. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004;89:1187-93.
3. Ceci A, Felisi M, De Sanctis V, De Mattia D. Pharmacotherapy of iron overload in thalassaemic patients. Expert Opin Pharmacother 2003;4:1763-74.
4. Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. Br J Haematol 2002;118:330-6.
5. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica 2003;88:489-96.
6. Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006;107:3733-7.
7. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in β-thalassaemia. Lancet 2002; 360:516-20.
8. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, et al. Randomized controlled trial of deferiprone or deferoxamine in β-thalassemia major patients with asymptomatic myocardial siderosis. Blood 2006;107:3738-44.
9. Loukopoulos D. Combined therapy with deferiprone and desferrioxamine in thalassemia major. Haematologica 2005; 90:1304-5.
10. Origa R, Bina P, Agus A, Crobu G, Defraia E, Dessi C, et al. Combined therapy with deferiprone and desferrioxamine in thalassemia major. Haematologica 2005;90:1309-14.