Blood Cells, Molecules, and Diseases 42 (2009) 247–251

Contents lists available at ScienceDirect

Blood Cells, Molecules, and Diseases

journal homepage: www.elsevier.com/locate/ybcmd

Improving survival with deferiprone treatment in patients with thalassemia major: A prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies

Aurelio Maggio [a,*], Angela Vitrano [a], Marcello Capra [b], Liana Cuccia [b], Francesco Gagliardotto [b], Aldo Filosa [c], Carmelo Magnano [d], Michele Rizzo [e], Vincenzo Caruso [d], Calogera Gerardi [f], Crocetta Argento [g], Saveria Campisi [h], Francesco Cantella [i], Francesca Commendatore [j], Domenico Giuseppe D'Ascola [k], Carmelo Fidone [l], Angela Ciancio [m], Maria Concetta Galati [n], Gaetano Giuffrida [o], Rocca Cingari [o], Giovanni Giugno [p], Turi Lombardo [q], Luciano Prossomariti [r], Roberto Malizia [s], Anna Meo [t], Gaetano Roccamo [u], Maria Antonietta Romeo [v], Pietro Violi [w], Paolo Cianciulli [x], Paolo Rigano [a]

[a] U.O.C. "Ematologia II con Talassemia", A.O. "V. Cervello", Palermo, Italy
[b] U.O.C. 7a Pediatria per le Emopatie Ereditarie, Centro di Prevenzione Diagnosi e Cura della Talassemia, A.O. "G. Di Cristina", Palermo, Italy
[c] U.O.C. Pediatria, A.O. Cardarelli, Napoli, Italy
[d] Unità Operativa Dipartimentale Talassemia, P.O. "S. Luigi-Currò" – ARNAS Garibaldi, Catania, Italy
[e] U.O.C. Ematologia, A.O. "S. Elia", Caltanissetta, Italy
[f] U.O.S. di Talassemia, A.O.O.C.R.,Sciacca, Italy
[g] U.O.C. Medicina Trasfusionale, A.O. "S. Giovanni di Dio", Agrigento, Italy
[h] U.O.S. Centro Microcitemia, A.O. Umberto I, Siracusa, Italy
[i] U.O.C. Medicina Trasfusionale, A.O."V. Emanuele" III, Gela (CL), Italy
[j] U.O.S. di Talassemia, ASL. 8 Siracusa, Lentini, Italy
[k] Centro Microcitemia, A.O. B.M.M., Reggio Calabria, Italy
[l] U.O. C. Centro Trasfusionale, A.O. "M. Paternò Arezzo", Ragusa, Italy
[m] U.O.S. Centro Microcitemia, A.O.C. Madonna delle Grazie, Matera, Italy
[n] Dipartimento Ematologia, A.O. "Pugliese Ciaccio" Catanzaro, Italy
[o] U.O.C. Ematologia, A.O. Ferrarotto, Catania, Italy
[p] U.O. Talassemia, A.O. Gravina e Santo Pietro, Caltagirone, Italy
[q] U.O.C. di Ematologia con Talassemia, A.O. "S. Bambino", Catania, Italy
[r] Centro Regionale per la Cura delle Microcitemie, A.O.Cardarelli, Napoli, Italy
[s] U.O.C. Pediatria, A.O. "Villa Sofia", Palermo, Italy
[t] U.O. Genetica ed Immunologia Pediatrica,Policlinico "G. Martino", Messina, Italy
[u] Centro Microcitemia, P.O. S.Agata di Militello, Messina, Italy
[v] U.O.C. Talassemia, Clinica Pediatrica I,Università degli Studi di Catania, A.O. Policlinico, Catania, Italy
[w] Casa Sollievo della Sofferenza, Istituto di Ricovero e Cura a Carattere Scientifico, U.O. Centro della Microcitemia, San Giovanni Rotondo (Foggia), Italy
[x] U.O. Talassemia, A.O. "S. Eugenio", Roma, Italy

ARTICLE INFO

Article history:
Submitted 23 December 2008
Revised 8 January 2009
Available online 23 February 2009

(Communicated by
G. Stamatoyannopoulos, M.D., Dr. Sci.,
8 January 2009)

Keywords:
thalassemia survival
chelation treatment
thalassemia trial
thalassemia major

ABSTRACT

The prognosis for thalassemia major has dramatically improved in the last two decades. However, many transfusion-dependent patients continue to develop progressive accumulation of iron. This can lead to tissue damage and eventually death, particularly from cardiac disease. Previous studies that investigated iron chelation treatments, including retrospective and prospective non-randomised clinical trials, suggested that mortality, due mainly to cardiac damage, was reduced or completely absent in patients treated with deferiprone (DFP) alone or a combined deferiprone–deferoxamine (DFP–DFO) chelation treatment. However, no survival analysis has been reported for a long-term randomised control trial. Here, we performed a multicenter, long-term, randomised control trial that compared deferoxamine (DFO) versus DFP alone, sequential DFP–DFO, or combined DFP–DFO iron chelation treatments. The trial included 265 patients with thalassemia major, with 128 (48.3%) females and 137 (51.7%) males.

No deaths occurred with the DFP-alone or the combined DFP–DFO treatments. One death occurred due to graft versus host disease (GVHD) in a patient that had undergone bone marrow transplantation; this patient was censored at the time of transplant. Only one death occurred with the DFP–DFO sequential treatment in a

* Corresponding author. Fax: +39 091 6880828.
E-mail address: aureliomaggio@virgilio.it (A. Maggio).

1079-9796/$ – see front matter
doi:10.1016/j.bcmd.2009.01.002

patient that had experienced an episode of heart failure one year earlier. Ten deaths occurred with the deferoxamine treatment.
The main factors that correlated with an increase in the hazard ratio for death were: cirrhosis, arrhythmia, previous episode of heart failure, diabetes, hypogonadism, and hypothyroidism. In a Cox regression model, the interaction effect of sex and age was statistically significant (p-value<0.013). For each increasing year of age, the hazard ratio for males was 1.03 higher than that for females (p-value<0.013).
In conclusion, the results of this study show that the risk factors for predicting mortality in patients with thalassemia major are deferoxamine-treatment, complications, and the interaction effect of sex and age.

Introduction

The prognosis for thalassemia major has dramatically improved in the past two decades. In the 1960s, regular blood transfusions became a standard treatment to maintain mean haemoglobin levels in the normal range. This gave good quality of life in the short term, but led to death from transfusional iron overload between 12 and 24 years of age [1]. In 1976, it was shown that a subcutaneous infusion of deferoxamine (DFO) using a portable syringe driver could stabilise body iron load at around 0.3 mg/kg body weight. By 1980, a subcutaneous infusion at an average daily dose of 40–45 mg/kg/day (usually over 8 to 12 h, five nights per week) had become standard care [2]. Regular blood transfusions and iron chelation with deferoxamine have changed the prognosis of the disease [3].

However, many transfusion-dependent patients continue to develop progressive accumulation of iron. This can lead to tissue damage and eventually death. Moreover, a recent survival analysis suggested that cardiac disease is responsible for 70% of the deaths in patients treated with deferoxamine [4].

In 1995, a new oral chelator, deferiprone (DFP; 1,2-dimethyl-3-hydxoxypyridin-4-one) became available for clinical use [5]. Previous papers, including retrospective, natural history, and prospective non-randomised clinical trials, suggested that mortality, due mainly to cardiac damage, was reduced or completely absent in patients treated with DFP alone or with deferiprone–deferoxamine (DFP–DFO) combined chelation treatment [4,6–10]. However, no prospective survival analysis has been reported comparing deferoxamine alone versus DFP alone or sequential or combined DFP–DFO treatments in a randomised control trial.

Here we report a prospective survival analysis during a long-term multicenter randomised trial among patients receiving different iron chelation treatments for thalassemia major.

Patients and methods

Design

The trial was designed as a follow-up of patients with thalassemia major that had been included in a multicenter, randomised, open-label trial comparing long-term sequential DFP–DFO versus DFP alone treatment (Fig. 1). The trial was performed on behalf of the Italian Society for the Study of Thalassemia and Hemoglobinopathies (SoSTE; www.soste.org). The investigators initiated, carried out, and controlled the trial. The trial was conducted without the influence of our non-commercial sponsor.

Patients

Consecutive patients with thalassemia major who were admitted to 25 SoSTE centers in Italy between September 30, 2000 and January 31, 2008 were considered eligible for the trial if they were over 13 years of age. Parents gave informed consent for patients between 13 and 18 years of age. The data were collected at the coordinating center (A.O.V. Cervello, U.O.C. di Ematologia II, Palermo, Italy). All the patients received DFO by subcutaneous infusion at an average daily dose of 40–45 mg/kg/day (usually over 8 to 12 h, five nights per week) before the date of randomisation.

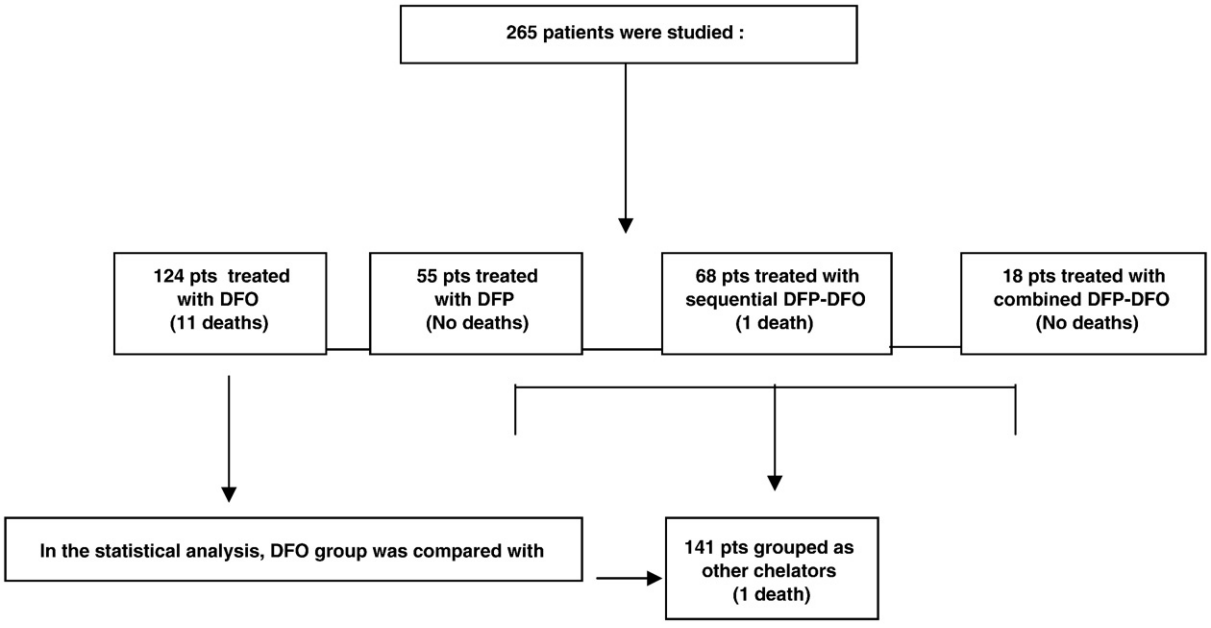

Fig. 1. Trial profile.