Leukemia Research 56 (2017) 88–95

Contents lists available at ScienceDirect

Leukemia Research

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

Relation between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndromes: Registry analysis at 5 years

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ARTICLE INFO

Article history:
Received 23 September 2016
Received in revised form 23 January 2017
Accepted 30 January 2017
Available online 31 January 2017

Keywords:
Iron chelation
Iron overload
Myelodysplastic syndromes

ABSTRACT

Prospective data are needed to ascertain the impact of iron chelation therapy in patients with myelodysplastic syndromes. The present 5-year prospective registry analysis was conducted to compare clinical outcomes between chelated and nonchelated patients with lower-risk myelodysplastic syndromes and transfusional iron overload. In an interim analysis at 24 months, we previously reported that chelation therapy was associated with longer median overall survival and a tendency toward longer leukemia-free survival and fewer cardiac events. In the present report, we detail findings from the final analysis at 5 years. We confirm, at the conclusion of this 5-year, prospective, non-interventional study, that overall survival was significantly longer in patients who received iron chelation therapy vs those who did not. Causes of death in the overall population were predominantly myelodysplastic syndromes/acute myeloid leukemia followed by cardiac disease. Time to progression to acute myeloid leukemia was also significantly longer in patients receiving chelation therapy, and significantly fewer patients progressed to leukemia vs those not receiving chelation therapy. Limitations of the study include a potential for clinical bias, as patients with longer predicted survival may have been chosen for chelation therapy, the differences present in concomitant conditions at baseline, and the possibility that some high-risk patients were not identified due to limited cytogenetic classification.

Contents

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FAB, French-American-British; HR, hazard ratio; ICT, iron chelation therapy; IO, iron overload; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; RBC, red blood cell; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.leukres.2017.01.033

1. Introduction

Patients with myelodysplastic syndromes (MDS) have deficiencies in hematopoiesis and are at increased risk for progression to acute myeloid leukemia (AML) [1–3]. As many as 80% of patients with MDS will develop anemia, and transfusion dependency is common throughout the course of disease [2,3]. Each unit of red blood cells (RBCs) is estimated to contain 200–250 mg of iron, and since there is no physiologic mechanism for iron excretion, chronic transfusion of patients with MDS is associated with risk for iron overload (IO) [2–4]. In retrospective studies, transfusion-dependent patients with MDS had significantly shorter survival than those who were not transfusion dependent (hazard ratio [HR] = 2.16; $P < 0.001$); leukemia-free survival was also shorter in the transfusion-dependent group (HR = 2.02; $P < 0.001$) [5]. Development of secondary IO (defined in the study as serum ferritin >1000 ng/mL) resulted in an adverse impact on survival, which was also demonstrated in the transfusion-dependent patients: For each 500-ng/mL increase above the defined threshold, a 1.3-fold increase in the risk for death was observed ($P = 0.003$) [5]. Similar findings were reported by Cermak et al., who found a significant impact of transfusion dependency on survival in a subset of patients with early MDS [4]. Complications of transfusional IO include cardiac, hepatic, and endocrine organ damage. In particular, cardiac complications have been reported as a frequent cause of death in patients with MDS with a high transfusional burden [2–4,6]. Therefore, the use of iron chelation therapy (ICT) has been considered a treatment to reduce IO and its associated complications in transfusion-dependent patients with MDS. The results of several retrospective and observational studies in MDS populations have suggested that ICT is associated with improved survival in patients with MDS with IO [7–13,21–23].

Oral therapies such as deferasirox are available for ICT and have been investigated in patients with MDS and evidence of IO. Results of these studies have generally shown substantive reductions in total iron burden, as assessed by serum ferritin, despite continued transfusional requirements, although they have not been designed nor sufficiently powered to determine the impact on IO-related morbidity or mortality [14–16]. A prospective, placebo-controlled study (TELESTO) is examining the use of ICT with deferasirox in patients with MDS with low and intermediate-1 risk MDS and transfusional IO [17]. Results of the TELESTO study are anticipated in late 2017, but prospective data on the relation of ICT to morbidity and mortality in this population are presently lacking. Previously, we reported data from a 5-year registry of 599 lower-risk patients with MDS in the United States. The goal of the registry study was to provide prospective data on clinical and safety parameters in chelated and nonchelated transfusion-dependent patients with MDS with IO [18]. At the 24-month interim analysis, we found that chelated patients had significantly longer median survival compared with nonchelated patients (99.3 vs 52.2 months; $P < 0.0001$). There was also a trend toward less progression to AML, and fewer newly diagnosed or progressive cardiac conditions after study entry in chelated patients relative to nonchelated patients [18]. Here, we present the final 5-year analysis of clinical outcomes in this population of patients with lower-risk MDS with transfusional IO. Data on hematologic parameters, overall survival, and the time to AML transformation are presented. This work was presented in part at the 56th American Society of Hematology Annual Meeting and Exposition, December 6–9, 2014, San Francisco, CA.

2. Patients and methods

This prospective, 5-year, non-interventional study enrolled 599 patients from 118 centers across the United States. The primary objective of the study was to evaluate the impact of chelation on overall survival (up to 5 years) in iron overloaded patients with lower-risk MDS. The study was limited to patients aged ≥18 years with lower-risk MDS as determined by 1 of 3 MDS classification systems: World Health Organization (WHO), French-American-British (FAB), or International Prognostic Scoring System (IPSS). Eligible patients had transfusion-dependent IO, defined as ≥20 units of packed RBCs or an ongoing transfusion requirement of ≥6 units every 12 weeks, and/or a serum ferritin level >1000 ng/mL, and had lower-risk MDS. Patients classified as IPSS intermediate-1 risk were also eligible for enrollment in this study. Approved and experimental MDS therapies were permitted, and investigators in the study used institutional standard practices for MDS care and ICT. Analysis of patient outcomes was conducted as previously described, with patients defined as nonchelated, chelated (having received ICT at any point), or chelated for ≥6 months cumulatively. Subanalyses of patients who had received ≥6 months of ICT were preplanned in the study [18]. Follow up was performed at 6-month intervals and patients were observed for a maximum of 60 months, or until death. Demographics, survival, cause of death, leukemic transformation, serum ferritin, concomitant illnesses, transfusion requirements, and safety were included among the assessments [18]. Descriptive summaries were provided for demographic parameters (age, sex, race) and Eastern Cooperative Oncology Group (ECOG) performance status, as well as patient study completion status, time on study, concomitant conditions while in the study, MDS treatment, MDS status, cumulative duration of ICT, and RBC transfusions. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki and all patients gave written informed consent prior to enrollment.

3. Results

3.1. Baseline characteristics

The demographics and MDS risk status for all enrolled patients in the 3 groups (nonchelated, n = 329; chelated, n = 270; ≥6 months chelation, n = 203) are shown in Table 1. Patient demographics were typical of an MDS population and were mostly balanced across treatment groups. The median age was 76 years (range 21–99) across all study groups. Of the 599 enrolled patients, the majority were male (57.8%). The majority of patients in the study population were Caucasian (86.6%), 6.2% were Hispanic, 5.5% were African American, and 1.0% were Asian. Overall, 25.5% had an ECOG performance status of zero, 52.4% had ECOG performance status of 1, and 18.9% had ECOG performance status of 2. Overall median time from MDS diagnosis to study enrollment was 24.5 months (range 0–429.9): 18.6 months for the nonchelated group, 33.9 months for the chelated group, and 41.1 months for the ≥6 months chelated group. At diagnosis, 43.6% of patients were classified under the