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Improved survival in MDS patients receiving iron chelation therapy – A matched pair analysis of 188 patients from the Düsseldorf MDS registry

Judith Neukirchen*, Frank Fox, Andrea Kündgen, Kathrin Nachtkamp, Corinna Strupp, Rainer Haas, Ulrich Germing, Norbert Gattermann

Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine University, Düsseldorf, Germany

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ABSTRACT

MDS patients are prone to develop transfusional iron overload. Iron overload may partly explain why transfusion dependency is associated with a decreased likelihood of survival. Our matched-pair analysis included 94 patients on long-term chelation therapy and 94 matched patients without it. All patients had iron overload, defined as serum ferritin (SF) above 1000 ng/ml or a history of multiple transfusions and SF ≥ 500 ng/ml. Median SF was 1954 ng/ml in chelated and 875 ng/ml in non-chelated patients. The difference in median survival (74 vs. 49 months, respectively; $p = 0.002$) supports the idea that iron chelation therapy is beneficial for MDS patients.

1. Introduction

Patients with myelodysplastic syndromes (MDS) suffer from peripheral blood cytopenias as a result of bone marrow failure. Besides medullary blast count and karyotype, transfusion dependency has been identified as an important prognostic factor [1,2] and has therefore been integrated into the WHO-classification based prognostic scoring system (WPSS) [3].

Despite new treatment options, many MDS patients rely on red blood cell transfusions. Chronic transfusion therapy causes iron overload. Recently, a large retrospective analysis showed that iron overload, defined as a serum ferritin >1000 ng/ml, was a significant prognostic factor for OS and leukemia-free survival in MDS [1]. On multivariate analysis, the influence of iron overload was independent of transfusion requirement.

If iron overload shortens the survival of patients with MDS, iron chelation (IC) should do the opposite. This view is supported by a partly retrospective and partly prospective observational study by Rose et al. [4] showing that patients with an IPSS low or intermediate-1 risk profile who received iron chelation therapy lived longer than patients who did not. However, there are as yet no results available from randomized clinical trials to confirm such a survival benefit. We performed a retrospective matched-pair analysis drawing on the data base of the Düsseldorf MDS registry.

2. Methods

At the time of patient selection the Düsseldorf MDS registry included 3552 patients, diagnosed between 1975 and 2008. For matched-pair analysis [5] we identified 94 polytransfused MDS patients who had been receiving long-term chelation therapy. The registry was then searched for matching partners who received supportive care, including growth factors, but neither iron chelators nor disease-modifying drugs. The following characteristics were used for matching: age at diagnosis (±5 years), gender, MDS type according to WHO classification, and IPSS score. We chose 94 patients fulfilling all selection criteria. The cut-off date for this report was June 30, 2009. To deal with confounding variables, each patient was paired with a randomly chosen matched control. Cases and controls were stratified according to chelation treatment [6].

3. Results

Patient characteristics are shown in Tables 1a and 1b. All 188 patients showed iron overload, defined as a serum ferritin ≥1000 ng/ml, or a history of multiple transfusions and a serum ferritin ≥500 ng/ml. All ferritin levels were measured at the time of referral to our center, which was usually early after diagnosis. The proportion of heavily transfusion-dependent patients was largest among patients with del(5q), RCMD, and refractory anemia with excess blasts (RAEB-I and -II). At least 50% of patients with these diagnoses received transfusions of packed red blood cells (PRBC). Mean and median serum ferritin (SF) levels were also highest in patients with del(5q). SF levels were not correlated with gender or

* Corresponding author at: Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine University, Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany. Tel.: +49 211 8117720; fax: +49 211 8118853.
E-mail address: judith.neukirchen@med.uni-duesseldorf.de (J. Neukirchen).

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Table 1a
Clinical characteristics of chelated and non-chelated patients with MDS.

Parameter	Chelated	Non-chelated	*p*
Median age (range)	64 (18–82)	67.5 (33–89)	0.005
Gender	48% w	42% w	ns
Ferritin (mean)	2400	980	0.005
Karnofsky index < 60%	25%	31.5%	ns
Transfusions at diagnosis	75%	85%	ns
Platelets (μl)	229,000	231,000	ns
ANC (μl)	2500	3600	ns
Hemoglobin (g/dl)	8.7	9.0	ns
Medullary blast count	4%	4%	ns
Karyotype risk category			
Low risk	71%	76%	
Intermediate	18%	12%	ns
High risk	11%	12%	
Ferritin > 1000 ng/ml	80%	78%	ns
Ferritin > 500 ng/ml and transfusions	20%	22%	ns
AML development	12.9%	14%	ns
Proportion of patients who died during the observation period	56%	60%	ns
Death due to infections	35%	13%	0.03
Death due to bleeding	4.5%	9.5%	
Other causes of death	60.5%	77%	
Comorbidities			
Lung	7%	9%	ns
Heart	23%	43%	ns
Kidney	3.5%	0%	ns
Liver	2%	12%	0.039
Solid tumors	11%	12%	ns

IPSS risk group. Chelation therapy was started at a median of 21 months after diagnosis (range 0–212 months).

53 patients in the IC group received deferoxamine monotherapy and 47 received deferasirox monotherapy. Deferoxamine followed by deferasirox was used in 14 patients, and deferoxamine followed by deferiprone in 3 patients. Mean duration of chelation therapy was 39 months for deferoxamine and 28 months for deferasirox. There were some patients on long-term treatment with deferoxamine, lasting much longer than any treatment period with deferasirox, simply owing to the time that the latter has been available. Overall, in our hands, deferasirox has not been more difficult to handle than deferoxamine, which poses compliance problems due to its cumbersome parenteral administration. The majority of deferoxamin-treated patients received the drug by continuous infusion overnight, but there were also some patients receiving deferoxamine as regular twice daily subcutaneous bolus injections.

Among patients receiving chelation therapy, 56% died during the observation period, as compared to 60% in the group of patients receiving supportive care only (Fig. 1a). Median survival was 75 months in the IC group and 49 months in the supportive care group ($p = 0.002$). There was no significant difference regarding risk of AML evolution (Fig. 1b). Cumulative risk of AML transformation in the IC vs. supportive care group was 10% and 12% two years after diagnosis, and 19% and 18% five years after diagnosis, respectively ($p = 0.73$).

There was no significant difference in median survival between chelated and non-chelated individuals in the cohort of patients with higher-risk MDS, whereas a significant difference was found in the lower-risk group ($p = 0.008$). Causes of death not related to MDS were slightly more frequent in the chelated patient group, but firm conclusions could not be drawn since death certificates were not available in many patients.

Data on response to IC were available for 31 patients with stable MDS and ongoing transfusion dependency. Among these, 21 showed stable or decreasing serum ferritin during IC therapy. These patients had a significant survival benefit compared to patients with increasing SF (Fig. 2).

Table 1b
MDS types and risk profile according to WHO and IPSS classification, respectively, in the iron chelated patients ($n = 94$).

Classification system	*n* (%)
WHO	
MDS with del(5q)	22 (23)
RA	6 (6)
RARS	9 (10)
RCMD	40 (43)
RAEB-I	8 (9)
RAEB-II	4 (4)
CMML	5 (5)
IPSS	
Low	35 (37)
Intermediate-1	43 (46)
Intermediate-2	13 (14)
High	3 (3)

RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; CMML, chronic myelomonocytic leukemia.

4. Discussion

In the field of thalassemia, it is well established that transfusional iron overload limits life expectancy due to toxic effects on heart, liver and other organs. In patients with MDS, the situation is more difficult to understand. Chronic transfusion therapy is clearly associated with a decreased likelihood of overall survival and leukemia-free survival [1,2]. There is a dose-dependent effect of transfusion requirement, and a similar dose-dependent effect of serum ferritin levels, on overall and leukemia-free survival.

The similar impact of transfusion requirement and serum ferritin levels could be interpreted as evidence that transfusion dependency causes iron overload, which then worsens the prognosis. However, the data can also be interpreted the other way round: transfusional iron overload reflects severe bone marrow disease as the real cause of shortened survival. Both interpretations are probably correct, because multivariate analyses have shown that iron overload has independent prognostic impact, even if transfusion need is taken into account [1,2].

Assuming that iron overload diminishes the likelihood of survival in MDS, chelation therapy should have an oppositive effect.