Myelodysplastic Syndrome in Hemodialysis Patients

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Anemia is a common feature in late-stage chronic kidney disease (CKD), especially in hemodialysis (HD) patients, with the main cause being erythropoietin (EPO) deficiency.[1] To date, erythropoiesis-stimulating agents (ESAs) are the cornerstones of anemia therapy in HD patients. Unfortunately, a significant proportion (20%−25%) of HD patients do not respond as well as expected to ESAs. In these patients, multiple factors that may contribute to EPO hyporesponsiveness and anemia exacerbation have been identified.[2] Myelodysplastic syndrome (MDS) is a rare disease occurring mainly in elderly individuals. This syndrome comprises a heterogeneous group of clonal and malignant myeloid disorders, defined by peripheral cytopenia, bone marrow failure, and morphologic dysplasia in 1 or more hematopoietic lineages.[3] Its incidence in the hemodialysis population has not been studied.

In the present study, we report for the first time a historical observational study of 20 HD patients with MDS. We stratified 2 different MDS populations based on their distinct EPO hyporesponsiveness pattern and clinical evolution.

The study included 20 patients (5 women and 15 men) from 9 hemodialysis centers from 2002 to 2018 (see Supplementary Materials and Methods). Ten patients had MDS diagnosed before dialysis onset (MDS-1), and 10 had MDS diagnosed after dialysis onset (MDS-2). Demographic characteristics are shown in Table 1. MDS-EB, MDS with excess blasts (MDS-EB) was diagnosed in 3 patients (15%), MDS with multilineage dysplasia (MDS-MLD) in 7 (35%), MDS-SLD, MDS with single-lineage dysplasia (MDS-SLD) in 4 (30%), MDS with ring sideroblasts (MDS-RS) in 2 (10%), and chronic myelomonocytic leukemia (CMML) in 4 patients (all patients were in MDS-1). The International Prognostic Scoring System Revised (IPSS-R) score was mostly low for 10 patients (4 in MDS-1 group and 6 in MDS-2 group). Baseline characteristics of the control group are shown in Supplementary Table S1.

In the MDS-1 group, MDS was diagnosed 1.4 (0.05−4.07) years before dialysis onset. During the first year of dialysis, median hemoglobin level increased from 9.1 (8−10) to 9.9 (9.3−11.3) g/dl ($P = 0.2$) and median ferritin level from 146.5 to 461 ng/ml ($P = 0.054$). (Table 2, and Figure 1a). The median EPO dose increased from 150 (93.6−263.3) to 256.5 (98.4−482.9) IU/kg per week ($P = 0.052$), compared to control values, 124.5 (0–672.3) versus 74.3 (0–444.4) IU/kg per week ($P = 0.003$) (Supplementary Table S2). The MDS-1 patients presented with moderate thrombocytopenia but no sign of bone marrow failure (Figure 1c). The erythropoietin resistance index (ERI), which reflects the EPO responsiveness, was similar in both groups at the onset of dialysis. The median ERI increased only in MDS-1 patients, from 19 (9.4−29.5) to 25.7 (9.7−42.7) ($P = 0.08$), compared with controls, from 12.2 (8.5−19.2) to 6.7

Table 1. Baseline characteristics

	All patients	MDS-1	MDS-2	*P* value
Number of patients (n)	20	10	10	
Sex (male/female)	15/5	6/4	9/1	0.34
Median age at the onset of dialysis (yr)	73.8 [65.6–78.3]	76.2 [69.0–83.5]	73.7 [64.2–75.9]	0.20
Median age at MDS diagnosis (yr)	74.7 [70.2–79.9]	74.1 [68.0–81.7]	76.6 [69.2–79.3]	0.86
Median follow-up duration after MDS diagnosis (yr)	5.4 [1.2–6.9]	3.4 [0.8–6.0]	1.1 [0.6–4.8]	0.53
Nephropathy (n)				
Diabetes	7	5	2	0.34
Hypertension	5	4	1	0.30
Interstitial	1	1	0	1
Others	7	0	7	0.003
Comorbidities (n)				
Hypertension	17	9	8	1
Diabetes	9	4	5	1
Liver disease	4	0	4	0.08
Dialysis modality (n)				
HD	12	5	7	0.64
HDF	8	5	3	0.64
MDS subtype (n)				
MDS-EB	3	1	2	1
MDS-MLD	7	2	5	0.34
MDS-SLD	4	2	2	1
MDS-RS	2	1	1	1
CMML	4	4	0	0.08
IPSS (n)				
Available	15/16	5/6	10/10	0.22
Low	12	4	8	1
High	3	1	2	
IPSS-R (n)				
Available	14/16	4/6	10/10	0.65
Low (≤3)	10	4	6	0.33
Intermediary (3.5–4.5)	2	0	2	0.33
High (≥5)	2	0	2	

CMML, chronic myelomonocytic leukemia; HD, hemodialysis; HDF, hemodiafiltration; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System Revised; MDS, myelodysplastic syndrome; MDS-1, onset of dialysis after diagnosis of MDS; MDS-2, onset of dialysis before diagnosis of MDS; MDS-EB, MDS with excess blasts; MDS-MLD, MDS with multi-lineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-SLD, MDS with single-lineage dysplasia.
Results expressed as median [interquartile range].

(3.7−10.5) ($P < 0.001$). Hemoglobin level in MDS-1 patients was still lower than in controls ($P = 0.009$).

In MDS-2 patients, the median time before diagnosis was 3.8 (1.5−4.6) years after the beginning of dialysis.

Table 2. Biological data at M0 (onset of dialysis) and at M12 (1 year after) in MDS-1 group

	M0 (onset of dialysis)	M12 (1 yr after)	*P* value
Hemoglobin (g/dl)	9.1 [8–10]	9.9 [9.3–11.3]	0.2
MCV (fl)	93.0 [86.1–98.8]	101.6 [97.9–105.8]	0.03
Neutrophils (/mm^3)	3.3 [1.4–4.6]	3.4 [2.3–4.6]	0.3
Platelets (/mm^3)	134.5 [59.7–178]	121 [52.5–185.2]	0.6
Reticulocytes (/mm^3)	56 [24–65.1]	88.9 [71.1–117.6]	0.4
C-reactive protein (mg/l)	10.3 [4.3–11.8]	6 [1–19]	0.3
Iron (µmol/l)	9 [6.4–16]	17.1 [11.2–24.4]	0.006
Ferritin (µg/l)	146 [71.5–280.5]	461.5 [261.5–871.5]	0.054
TSAT (%)	19 [12.5–42]	40 [25.7–69]	0.003
PTH (pg/ml)	132.5 [69.7–447.3]	181 [118.5–741.5]	0.9
EPO (UI/kg per week)	150 [93.6–263.3]	256.5 [98.4–482.9]	0.052
ERI	19 [9.4–29.5]	25.7 [9.7–42.7]	0.08

EPO, erythropoietin; ERI, erythropoietin resistance index; MCV, mean corpuscular volume; PTH, parathyroid hormone; TSAT, transferrin saturation.

The median hemoglobin level was 8.8 (7.3−10.5) g/dl, and the median reticulocyte count was 54.5 (10.7−86.5)/mm^3 (Table 3). Most (7/10) MDS-2 patients had thrombocytopenia (median platelet count 65.0 [40.7–179.2]/mm^3) and neutropenia (1.8 [0.6–4.2]/mm^3), and 4 had pancytopenia. One year after diagnosis, median hemoglobin level rose to 10.6 (9.1−11.6) g/dl ($P = 0.37$) despite a similar ERI (29.7 vs. 29.6, $P = 0.3$). All patients with an intermediate or high IPSS-R score were in this group. Two patients in the MDS-1 and 2 in the MDS-2 group were dependent on red blood cell transfusion. Principal component analysis (PCA) was used to investigate which biological parameters contributed the most to each profile (MDS-1, MDS-2, and controls) (Figure 1 and Supplementary Materials and Methods). We observed that EPO dose (correlation factor = 0.9855) and thrombocytopenia (correlation factor = −0.9959) were the 2 factors that contributed the most, according to the correlation circle (Figure 1d).

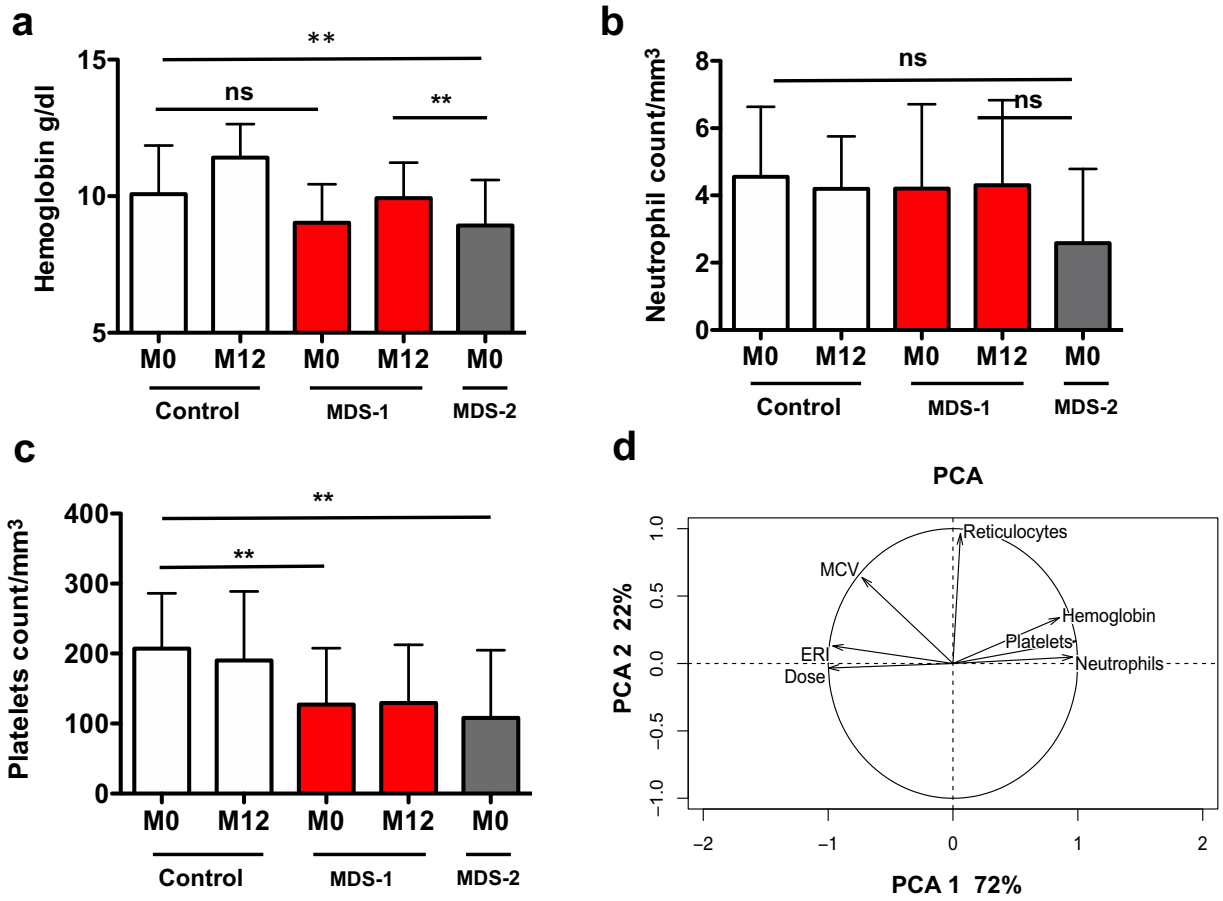

Figure 1. Correlation data in onset of dialysis after diagnosis of MDS (MDS-1) and onset of dialysis before diagnosis of MDS (MDS-2) groups. (a) Neutrophil, (b) hemoglobin, and (c) platelet counts in MDS-1 patients and controls at M0 and M12 of dialysis, and in MDS-2 patients at diagnosis (M0). Data are expressed as mean ± SD. $^{**}P < 0.01$; ns, nonsignificant (Mann–Whitney test). Principal component analysis (PCA) was used to define which biological parameters contributed the most to each profile (MDS-1, MDS2, and control). (d) Variable correction plots. ERI, erythropoietin resistance index; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome.

The survival rate at the last follow-up was 50% in MDS-1 and 60% in MDS-2 patients (Figure 2). In MDS-1, patients died with a median of 5.8 (3.7–6.9) years after diagnosis and 1.4 (1–4.1) years after dialysis onset, mostly from hematological complications. Three of the CMML patients died of hematological complications within 2 years of dialysis onset; 2 of them presented with leukemic progression. Four MDS-2 patients died within a median of 1.2 (0.5–5.8) years after diagnosis (1 leukemic

Table 3. Biological data, at M0 (MDS diagnosis) and at M12 (1 year after) in MDS-2 group

	M0 (at MDS diagnosis)	M12 (at 1-yr follow-up)	*P* value
Hemoglobin (g/dl)	8.8 [7.3–10.5]	10.6 [9.1–11.6]	0.37
MCV (fl)	96 [90–102.3]	96 [88.8–102.8]	0.8
Neutrophils (/mm^3)	1.8 [0.6–4.2]	4 [1.5–6.7]	0.1
Platelets (/mm^3)	65 [40.7–179.2]	53 [47.2–247.5]	0.6
Reticulocytes (/mm^3)	54.5 [10.7–86.5]	78 [37.4–95]	0.8
C-reactive protein (mg/l)	7 [2.5–14.5]	7 [3.9–55]	0.3
Iron (µmol/l)	16.1 [13–27.5]	13.6 [10.2–15.7]	0.3
Ferritin (µg/l)	566 [394.3–902]	268 [113–487]	0.03
TSAT (%)	43 [30–67]	26 [19–54]	0.6
PTH (pg/ml)	163 [86–240]	145 [131.5–333.5]	0.9
EPO (UI/kg/week)	270.9 [188.2–363.9]	306.4 [135.8–801.9]	0.26
ERI	29.6 [22.7–40.3]	29.7 [12.1–84.4]	0.3

EPO, erythropoietin; ERI, erythropoietin resistance index; MCV, mean corpuscular volume; PTH, parathyroid hormone; TSAT, transferrin saturation.
Results are expressed as median [interquartile range].

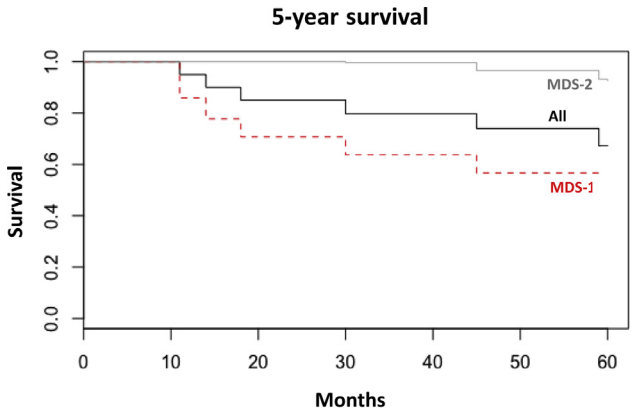

Figure 2. Survival after 5 years of dialysis. Graph represents survival after 5 years of dialysis for all patients (black), onset of dialysis after diagnosis of MDS (MDS-1) patients (red), and onset of dialysis before diagnosis of MDS (MDS-2) patients (gray). Difference in survival was not statistically significant ($P = 0.363$, log-rank test). MDS, myelodysplastic syndrome.

progression and 2 infectious complications). The IPSS-R score was 3 for 2 patients and 6 for the other patient.

CONCLUSION

To our knowledge, this is the first study of a cohort of HD patients with MDS. The latter are clonal hematopoietic stem cell disorders occurring in elderly individuals that usually lead to cytopenia. Bone marrow aspiration is mandatory to confirm the diagnosis by highlighting morphologic dysplasia in 1 or more hematopoietic lineages, as well as cytogenetic abnormality.[3] Anemia may be the only abnormal biological parameter in low-risk MDS patients.

Interestingly, we identified 2 different stratifications. In the first one, MDS was diagnosed during CKD stage 4 to 5 before the beginning of dialysis. These patients had lower-risk MDS, characterized by anemia with moderate thrombocytopenia. Despite commencing dialysis and the removal of uremic toxins, required EPO doses still increased during the first year of dialysis, as opposed to what is usually observed in HD patients without hematologic disorders.[4] However, few patients needed blood transfusions or developed bone marrow failure during the follow-up. In the second group, MDS was detected 2 years after the onset of dialysis. These patients showed typical features of bone marrow failure and required significant blood and/or platelet transfusions. This group had higher IPSS-R scores and survival was poor, as most of them died of MDS complications. We can hypothesize that only patients with recurrent severe anemia and/or thrombocytopenia were most likely to be diagnosed.

Our study emphasizes the difficulty in detecting MDS in dialysis patients. Because patients with a lower risk of MDS presented only with anemia, the incidence of MDS may be underestimated in elderly HD patients. Furthermore, their weekly weight-adjusted EPO dose (150−250 IU/kg per week) is under the commonly accepted threshold of EPO-resistance (300 IU/kg per week).[2] In contrast, the severity of MDS detected after the commencement of dialysis also reflected the delay in MDS diagnosis. These patients already had cytopenia, especially thrombocytopenia, which was a major cause of morbidity and mortality.[5] PCA suggested that thrombocytopenia and weekly ESA doses are the main factors that contribute to MDS profiles. Whether mild thrombocytopenia may be used as a surrogate marker of the disease remains to be determined. Finally, our study also suggests that special attention is required for persons with CMML, because the survival rate appears to be reduced after dialysis begins.

Our study may have several limitations. This is a retrospective cohort. The inclusion criteria for the MDS-1 group may be biased, because patients with more severe MDS would not be referred to a nephrologist or for dialysis. Conversely, patients with MDS-2 may undergo less intensive hematological follow-up because of clinical HD management.

Overall, this report emphasizes that MDS may occur in HD patients and is associated with a poor prognosis when detected after the onset of dialysis. MDS should be systematically considered for older (>75 years) HD patients who have recurrent anemia with high doses of erythropoietin and/or thrombocytopenia. As new treatment opportunities have recently emerged,[6–8] an improved collaboration between hematologists and nephrologists is required to identify and to manage these at-risk patients.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Materials and Methods.

Table S1. Demographic and biological characteristics of the control group.

Table S2. Comparison between controls and group 1.

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