OBJECTIVES: To evaluate the effects of epoetin (EPO) alfa treatment on overall survival, event-free survival and response duration in patients with myelodysplastic syndrome (MDS) who were treated at a haematological referral centre in northeastern Brazil.

METHODS: This was a retrospective cohort study of 36 patients diagnosed with MDS and treated with EPO alfa at 30,000 to 60,000 IU per week. Clinical data were collected from medical records. The events assessed were non-response to treatment and progression to acute myeloid leukaemia (AML). Statistical analyses were performed using GraphPad Prism 7 and SPSS 24 software.

RESULTS: The overall survival of patients who received EPO alfa treatment was 51.64%, with a median of 65 months of treatment, and the overall survival of this group was 100% during the first 24 months. We detected a 43.5-month median event-free survival, with a response rate of 80.5%. We observed responses from 25 to 175 months. Patients with transfusion dependence and those with a high-risk stratification, as determined by the International Prognostic Scoring System (IPSS), the Revised International Prognostic Scoring System (IPSS-R), the WHO classification-based Prognostic Scoring System (WPSS) and the WHO 2016, had a lower event-free survival than other patients.

CONCLUSIONS: Despite the wide use of EPO alfa in the treatment of anaemia in patients with MDS, the median response duration is approximately only 24 months. Our data provide encouraging results concerning the benefits of using EPO alfa for the improvement of the quality of life, as patients treated with EPO showed higher overall survival, event-free survival rates and longer response durations than have been previously described in the literature.

KEYWORDS: Myelodysplastic Syndrome; Recombinant Human Erythropoietin; Erythropoietin; Epoetin Alfa; EPO; EPO Alfa.
RESULTS

MATERIALS AND METHODS

This was a retrospective cohort study of 36 adult patients of both genders who were diagnosed with MDS and treated with EPO alfa. Follow-up occurred at the Haematology Department of the Hospital Universitário Walter Cantídeo (HUWC), Ceará, Brazil.

MDS was diagnosed according to the minimum criteria established at the Vienna Conference on MDS in 2006 (12). Patients were stratified according to their risk of progression to AML, according to the criteria of the World Health Organization 2016 (WHO 2016), the International Prognostic Scoring System (IPSS), the IPSS-R, and the WHO Classification-based Prognostic Scoring System (WPSS).

The response to treatment with EPO alfa was assessed according to the criteria established by the International Working Group (IWG) in 2006. The IWG defines a response as an increase in haemoglobin levels of 1.5 g/dL or a reduction in the transfusion requirement of four units after every 8 weeks of treatment (13).

Clinical data related to age, sex, blood count, treatment time, EPO alfa dose, transfusion dependence, myelogram, bone biopsy, and karyotype were collected from medical records.

Of the 42 patients treated with EPO alfa, six patients (14.3%) who did not have medical records available before treatment (which precluded any analysis of the evolution of the response) were excluded from the study.

Statistical analyses were performed using GraphPad Prism software version 7.0 and SPSS software version 24. The results are expressed as the mean ± standard error of the mean (SEM). A bivariate analysis was performed using the chi-square test, and the global survival and event-free survival analyses were performed using Kaplan-Meier curves. The events considered for the analysis were non-response to EPO alfa treatment and progression to AML. Values of $p <0.05$ were considered statistically significant.

RESULTS

The study population had a median age of 75 years (49-95 years) and had a predominance of females (55.56% female and 44.45% male). Most patients were classified as low/very low risk according to the IPSS-R (72.2%) and the WPSS (83.3%). Based on the WHO classification, the majority of patients were classified as MDS with multilineage dysplasia (MDS-MLD) (38.9%), followed by MDS with ringed sideroblasts (MDS-RS) (22.2%), MDS with dysplasia (MDS-SLD) (13.9%), MDS with excess blasts -1,2 (MDS-EB-1,2) (8.3%), and MDS with del (5q) isolated (11.1%); additionally, two patients (5.6%) progressed to AML (Table 1).

The median follow-up was 50 months, ranging from 2 to 175 months. The overall survival of patients who had a sustained response to EPO alfa treatment was 51.64%, with a median of 65 months of treatment. During the first 24 months, the overall survival of this group was 100%.

For the group of patients who were refractory to EPO alfa treatment, the overall survival was 14.28%, with a median of 3 months, which was significantly lower than the survival of the group who responded to EPO alfa ($p<0.0001$) (Figure 1).

Event-free survival throughout the follow-up period was 80.5% (Figure 2A and Table 1). Haemoglobin values increased significantly after 24 months and up to 175 months after the initiation of EPO alfa treatment, and the haemoglobin values remained higher than the values at the initiation of treatment ($p<0.001$) (Figure 3).

Patients with transfusion dependence ($p<0.0001$), those classified as high risk based on the IPSS ($p<0.0001$) and those classified as high/very high based on the IPSS-R ($p<0.0001$) and the WPSS ($p=0.0005$) had lower event-free survival (Figure 2B-2E) than the other patients.

The WHO classification was also able to stratify groups based on the response to treatment with EPO alfa. Event-free survival rates were lower in patients classified as MDS-RS, MDS-EB and del 5q than in patients classified as MDS-SLD and MDS-MLD ($p=0.03$) (Figure 2F).

After up to 175 months of treatment with EPO alfa, the event-free survival rates were greater than 93.3% in patients with a low/very low-risk stratification and no transfusion dependency (Figure 2B-2E).

A significant association was observed among the chi-square test for karyotype (very poor, poor, intermediate, and good, $p=0.0015$); normal, complex, trisomy, with del 5q and monosomy ($p=0.0205$); and the response to EPO alfa treatment (yes, no) (Table 1).

The main findings from the cytogenetic analysis showed normal karyotypes in 77.77% (28/36) of patients. Patients with a normal karyotype showed an 89.3% (25/28) response to EPO alfa treatment; in contrast, there was a 50% (4/8) response rate in patients with an altered karyotype.

Only 10.75% (3/28) of the patients with a normal karyotype did not respond to treatment with EPO alfa. None of the patients with a normal karyotype were transfusion dependent (Table 1).

Patients with a good karyotype were more common (88.9%, 32/36) than patients in the other cytogenetic risk groups of the IPSS-R. Only 15.6% of the patients with a good karyotype (1/6) were transfusion dependent, and 60% (3/5) of these patients did not respond to EPO alfa. Seventy-five percent of the patients with a 5q deletion responded to treatment (Table 1).

The poor and very poor cytogenetic risk groups (5.5%, 2/36), which corresponded to complex karyotypes, did not respond to EPO alfa (0%). The intermediate risk group (5.5%, 2/36) included one patient with a transfusion-dependent trisomy of chromosome 8, who also did not respond to EPO alfa treatment, and one patient with a monosomy of chromosome 18, who showed a non-transfusion-dependent response to treatment.

Only 33.33% (12/36) of patients had serum erythropoietin (sEPO) level data available in their medical records: 16.66% had sEPO levels $>200$ mU/mL, and 83.33% had levels $<200$ mU/mL. Patients who had elevated sEPO levels did not respond to treatment (100%). Most of the patients with sEPO levels $<500$ mU/mL (83.3%, 10/12) showed a response to EPO alfa. None of the patients had serum erythropoietin values $>500$ mU/mL (Table 1).

Most patients (91.66%, 33/36) started with low doses (30,000 IU) of EPO alfa that were administered weekly, and most patients showed a positive response to treatment
| Variable                      | Subgroup | Response | X² (p value) |
|-------------------------------|----------|----------|--------------|
|                               |          | Yes      | No           |
|                               |          | n/n total (%) | n/n total (%) |
|                               |          | 29 / 36 (80.5%) | 7/ 36 (19.4%) |
| SOCIO-DEMOGRAPHIC VARIABLES   |          |          |              |
| Gender                        |          |          |              |
| Female                        |          | 16 / 20 (80%) | 4 / 20 (20%) |
| Male                          |          | 13 / 16 (81.2%) | 3 / 16 (18.8%) |
| Age                           |          |          |              |
| <75                           |          | 11 / 15 (73.3%) | 4 / 15 (26.7%) |
| ≥75                           |          | 18 / 21 (85.7%) | 3 / 21 (14.3%) |
| ≤60                           |          | 1 / 1 (100%) | 0 / 1 (0%) |
| >60 - 75                      |          | 13 / 17 (76.5%) | 4 / 17 (23.5%) |
| >75 - 90                      |          | 13 / 16 (81.2%) | 3 / 16 (18.8%) |
| >90                           |          | 2 / 2 (100%) | 0 / 2 (0%) |
| BONE MARROW FINDINGS          |          |          |              |
| Cellularity of the bone marrow Hypocellular |          | 6 / 9 (66.7%) | 3 / 9 (33.3%) |
| Normocellular                 |          | 9 / 9 (100%) | 0 / 9 (0%) |
| Hypercellular                 |          | 14 / 18 (77.8%) | 4 / 18 (22.2%) |
| Ring sideroblasts Presence    |          | 21 / 24 (87.5%) | 4 / 24 (16.7%) |
| Absence                       |          | 8 / 12 (66.7%) | 4 / 12 (33.3%) |
| % Bone marrow blast           |          | 25 / 26 (96.1%) | 1 / 26 (3.9%) |
| >2%                           |          | 3 / 4 (75%) | 1 / 4 (25%) |
| 5% - 10%                      |          | 1 / 3 (33.3%) | 2 / 3 (66.7%) |
| >10%                          |          | 0 / 3 (0%) | 3 / 3 (100%) |
| PERIPHERAL BLOOD FINDINGS     |          |          |              |
| Haemoglobin IPSS-R (g/dL)*    |          |          |              |
| ≥10                           |          | 11 / 12 (91.7%) | 1 / 12 (8.3) |
| 8 - 10                        |          | 11 /13 (84.6%) | 2 / 13 (15.4%) |
| <8                            |          | 7 / 11 (63.6%) | 4 / 11 (36.4%) |
| ANC IPSS-R                   |          |          |              |
| ≤0.8                          |          | 6 / 7 (85.7%) | 1 / 7 (14.3%) |
| >0.8                          |          | 23 / 29 (79.3%) | 6 / 29 (20.7%) |
| Platelets IPSS-R             |          |          |              |
| ≥50                           |          | 2 / 4 (50%) | 2 / 4 (50%) |
| >50 - 100                     |          | 1 / 3 (33.3%) | 2 / 3 (66.7%) |
| >100                          |          | 26 / 29 (89.7%) | 3 / 29 (10.3%) |
| Cytopenias                    |          |          |              |
| ≤0                           |          | 16 / 17 (94.1%) | 1 / 17 (5.9%) |
| >5                           |          | 13 / 18 (68.4%) | 6 / 19 (31.6%) |
| CYTOGENETIC CHARACTERIZATION AND PROGNOSTIC IMPACT |          |          |              |
| Karyotype category 1          |          |          |              |
| Normal                        |          | 25 / 28 (89.3%) | 3 / 28 (10.7%) |
| Changed                       |          | 4 / 8 (50%) | 4 / 8 (50%) |
| Karyotype category 2          |          |          |              |
| Normal                        |          | 25 / 28 (89.3%) | 3 / 28 (10.7%) |
| Del.5q                        |          | 3 / 4 (75%) | 1 / 4 (25%) |
| Complex                       |          | 0 / 2 (0%) | 2 / 2 (100%) |
| Trisomy                       |          | 0 / 1 (0%) | 1 / 1 (100%) |
| Monosomy                      |          | 1 / 1 (100%) | 0 / 1 (0%) |
| Risk group IPSS-R             |          |          |              |
| Very low                      |          | 10 / 10 (100%) | 0 / 10 (0%) |
| Low                           |          | 16 / 16 (100%) | 0 / 16 (0%) |
| Intermediate                  |          | 3 / 5 (60%) | 2 / 5 (40%) |
| High                          |          | 4 / 4 (100%) | 4 / 4 (100%) |
| Very high                     |          | 0 / 1 (0%) | 1 / 1 (100%) |
| Risk group WPSS               |          |          |              |
| Very low                      |          | 12 / 13 (92.3%) | 1 / 13 (7.7%) |
| Low                           |          | 16 / 17 (94.1%) | 1 / 17 (5.9%) |
| Intermediate                  |          | 1 / 1 (50%) | 1 / 1 (50%) |
| High                          |          | 4 / 4 (100%) | 4 / 4 (100%) |
| Risk group IPSS               |          |          |              |
| Low                           |          | 18 / 18 (100%) | 0 / 18 (0%) |
| Intermediate 1                |          | 11/14 (78.6%) | 3 / 14 (21.4%) |
| Intermediate 2                |          | 0 / 1 (0%) | 1 / 1 (100%) |
| WHO 2016                      |          |          |              |
| MDS-SLD                       |          | 5 / 5 (100%) | 0 / 5 (0%) |
| MDS-RS                        |          | 6 / 8 (75%) | 2 / 8 (25%) |
| MDS-MLD                       |          | 14 / 14 (100%) | 0 / 14 (0%) |
| MDS-EB-1                      |          | 0 / 1 (0%) | 1 / 1 (100%) |
| MDS-EB-2                      |          | 1 / 2 (50%) | 1 / 2 (50%) |
| MDS with isolate (5q)         |          | 3 / 4 (75%) | 1 / 4 (25%) |
| Evolution to AML              |          | 0 / 2 (0%) | 2 / 2 (100%) |
| Transfusion dependence        |          |          |              |
| Yes                           |          | 2 / 7 (28.6%) | 5 / 7 (71.6%) |
| No                            |          | 27 / 29 (93.1%) | 2 / 29 (6.9%) |
Only one patient (33.33%, 1/3), who presented with a trisomy of chromosome 8, did not respond to high initial EPO alfa doses (60,000 IU) (Table 1). No statistically significant association was found between the response to treatment and the initial dose of EPO alfa ($p=0.5412$).

Some patients (82.75% 24/29) had a notable and surprisingly prolonged response, ranging from 25 to 175 months. All of these patients were transfusion independent, and the majority of these patients were classified by the WHO 2016 and IPSS-R as having a favourable response stratification.

Most patients (87.5%) had blasts $\leq 2\%$. Patients with a normal karyotype were predominant (83.3%). Only one patient had a karyotype with monosomy 18 (4.1%), and three karyotypes showed a 5q- deletion (12.5%). Most patients (95.8%) also had high platelet levels ($\geq 100,000$/mm3) (Table 2).

### DISCUSSION

Some multicentre studies that assessed the treatment of MDS patients with EPO reported response rates of approximately 30-50%, with a duration of 12-24 months (4,5,14,15). In contrast, the patients from our study centre had a higher response rate and a longer duration response.

Data are n (%) unless indicated otherwise. The relevant cut points were: *hemoglobin values of $< 8$ g/dL, 8 - $< 10$ g/dL, and $\geq 10$ g/dL; *platelet values of $< 50 \times 10^9$/L, 50 - $100 \times 10^9$/L and $\geq 100 \times 10^9$/L, and *absolute neutrophil counts (ANC) of $< 0.8 \times 10^9$/L versus $\geq 0.8 \times 10^9$/L. Cytopenias were defined as hemoglobin $< 11$ g/dL, absolute neutrophil count $< 0.8 \times 10^9$/L or platelets $< 100 \times 10^9$/L. Not all patients had data available, so percentages are based on twelve patients (n=12). Abbreviations: World Health Organization 2016 (WHO 2016); International Prognostic Scoring System (IPSS); Revised International Prognostic Scoring System (IPSS-R); the WHO classification-based Prognostic Scoring System (WPSS); absolute neutrophil count (ANC), and Standard deviation (SD).

Figure 1 - Overall survival (OS) of the study population treated with epoetin alfa.

(78.78%, 26/33). Only one patient (33.33%, 1/3), who presented with a trisomy of chromosome 8, did not respond to high initial EPO alfa doses (60,000 IU) (Table 1). No statistically significant association was found between the response to treatment and the initial dose of EPO alfa ($p=0.5412$).

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Some multicentre studies that assessed the treatment of MDS patients with EPO reported response rates of approximately 30-50%, with a duration of 12-24 months (4,5,14,15). In contrast, the patients from our study centre had a higher response rate and a longer duration response.

The results of two recent prospective, randomized, placebo-controlled trials of ESAs in MDS patients with anaemia (16,17)
Figure 2 - Survival analyses in the study population. (A) Event-free survival of the EPO alfa treated population. (B) Influence of transfusion dependence on event-free survival. (C-F) Influence of risk stratification on event-free survival.
were compared with our data. For example, the ARCADE (16)
study showed a significantly lower incidence of transfu-
sions during treatment in patients receiving darbepoetin
alfa than in those receiving a placebo ($p=0.008$), and the
darbepoetin-treated patients showed increased erythroid
response rates (14.7%; $p=0.016$). This erythroid response rate
was comparable to that reported for the EPOANE 3021 trial
(17), where 31.8% of the patients treated with EPO alfa

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**Table 2** - Patients with a response of greater than 24 months (25 to 175 months, n=24).

| Age | Karyotype | Transfusion dependence | IPSS-R | WHO 2016 | % Blasts MO | Haemoglobin (g/dL) | Platelets (×10^9/L) | Response time to EPO alfa (months) |
|-----|-----------|------------------------|--------|----------|------------|-------------------|-----------------|-------------------------------|
| 1   | 64 Good   | No                     | Very low | MDS-MLD | $\leq 2\%$ | $\geq 10$           | $\geq 100$       | 28                            |
| 2   | 95 Good   | No                     | Very low | MDS with isolated del 5q- | $\leq 2\%$ | $\geq 10$           | $\geq 100$       | 82                            |
| 3   | 94 Good   | No                     | Very low | MDS-RS  | $\leq 2\%$ | $\geq 10$           | $\geq 100$       | 145                           |
| 4   | 73 Good   | No                     | Low      | MDS-MLD | $\leq 2\%$ | $\geq 10$           | $\geq 100$       | 42                            |
| 5   | 70 Good   | No                     | Low      | MDS-MLD | $< 2\%$  | 8-10               | $\geq 100$       | 134                           |
| 6   | 75 Good   | No                     | Low      | MDS with isolated del 5q- | $< 2\%$  | 8-10               | $\geq 100$       | 75                            |
| 7   | 75 Good   | No                     | Low      | MDS-RS  | $< 2\%$  | 8-10               | $\geq 100$       | 30                            |
| 8   | 49 Good   | No                     | Low      | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 66                            |
| 9   | 76 Good   | No                     | Very low | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 83                            |
| 10  | 82 Good   | No                     | Low      | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 144                           |
| 11  | 82 Good   | No                     | Low      | MDS-EB-2 | 5%-10%  | 8-10               | $\geq 100$       | 73                            |
| 12  | 65 Good   | No                     | Very low | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 26                            |
| 13  | 74 Good   | No                     | Low      | MDS-RS  | $< 2\%$  | $\geq 10$           | $< 50$           | 127                           |
| 14  | 65 Good   | No                     | Very low | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 26                            |
| 15  | 70 Good   | No                     | Intermediary | MDS-RS | $> 2\% \cdot < 5\%$ | $< 8$      | $\geq 100$       | 175                           |
| 16  | 75 Good   | No                     | Very low | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 88                            |
| 17  | 86 Good   | No                     | Very low | MDS-MLD | $< 2\%$  | $\geq 10$           | $\geq 100$       | 65                            |
| 18  | 82 Good   | Deletion Sq-           | No       | MDS with isolated del 5q- | $< 2\%$  | $\geq 10$           | $\geq 100$       | 66                            |
| 19  | 68 Good   | No                     | Low      | MDS-MLD | $< 2\%$  | 8-10               | $\geq 100$       | 58                            |
| 20  | 73 Good   | No                     | Intermediary | MDS-MLD | $< 2\%$  | $< 8$              | $\geq 100$       | 66                            |
| 21  | 86 Good   | No                     | Low      | MDS-MLD | $> 2\% \cdot < 5\%$ | $\geq 10$ | $\geq 100$       | 35                            |
| 22  | 61 Intermediary | Monosomy | No    | MDS-SLD | $< 2\%$  | 8-10               | $\geq 100$       | 160                           |
| 23  | 80 Good   | No                     | Low      | MDS-RS  | $< 2\%$  | 8-10               | $\geq 100$       | 122                           |
| 24  | 81 Good   | No                     | Low      | MDS-RS  | $< 2\%$  | 8-10               | $\geq 100$       | 98                            |

* Hemoglobin values of $< 8$ g/dL, 8 - $< 10$ g/dL and $> 10$ g/dL; platelet values of $< 50 \times 10^9$/L, 50-100 $\times 10^9$/L and $> 100 \times 10^9$/L; Cytopenias were defined as hemoglobin $< 11$ g/dL; absolute neutrophil count $< 0.8 \times 10^9$/L; or platelets $< 100 \times 10^9$/L. Abbreviations: Revised International Prognostic Scoring System (IPSS-R); World Health Organization 2016 (WHO 2016); MDS with multidrug dysplasia (MDS-MLD), MDS with ringed sideroblasts (MDS-RS), MDS with dysplasia (MDS-SLD), MDS with excess blasts 2 (MDS-EB-2), and MDS with del (5q) isolated.
The characteristics of the patients who had significantly longer responses to treatment (25 to 154 months) confirmed the favourable prognosis and response of patients in the low-risk categories, which are characterized by no transfusion dependence, a normal karyotype, and a small number of bone marrow blasts (28). In patients with MDS, prognosis was better in those with a normal karyotype than in those with the presence of any structural or numerical changes. The karyotype also plays an important role in establishing the MDS diagnosis because during the course of the disease, cytogenetic methods are used to assess the response to therapy or to examine clonal evolution, which is a sign of disease progression (29).

Among the patients who did not respond to treatment, the predominant features included a complex karyotype, trisomy 8 and transfusion dependence. Patients with a complex karyotype showed an accumulation of progressive changes and greater disease aggressiveness, which were associated with an extremely unfavourable prognosis and a high propensity to transform into acute leukaemia within a short period of time. This observation was confirmed as a statistically significant association in our study (p=0.01), thereby demonstrating the importance of cytogenetic studies in the evolutionary monitoring of MDS. Patients with trisomy 8, as an isolated anomaly, have a significantly higher risk of leukaemic transformation than other patients, but the significance of the gain of an extra chromosome 8 is not yet fully understood (29,30).

In recent years, the value of serum erythropoietin in MDS has been explored in the literature as a predictor of the response to EPO. The role of sEPO levels as a prognostic risk factor in MDS also remains poorly understood. Despite the benefits of growth factor therapy, and of erythropoietin therapy in particular, studies have shown that sEPO levels (< 500 IU/L) are predictive of response (9,10,11). Patients who present with low sEPO levels associated with anaemia before treatment appear to respond more readily to EPO. These observations are further supported by the findings of other EPO studies (14,31). We observed a response in greater than 80% of patients with low sEPO levels. A limitation of the present study was the number of patients and the lack of availability of data on the sEPO levels in all patients; however, this examination is not covered by the Brazilian Unified Health System (SUS).

The results obtained in the present study support the importance of EPO alfa treatment for patients with MDS and suggest that the use of EPO alfa might achieve durable responses, thereby guaranteeing an improvement in the quality of life of these patients. However, the evaluation of each patient’s clinical characteristics, such as their risk stratification and transfusion dependence, is essential prior to the initiation of EPO alfa treatment.

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**AUTHOR CONTRIBUTIONS**

Moura ATG was responsible for planning the study, collecting data from medical records, building the database, analysing the data, performing
statistical analysis and drafting the manuscript. Duarte FB assisted with the planning of the study and the revision of the manuscript. Santos TEJ revised the manuscript. Lemes RPG assisted with the planning of the study and the revision of the manuscript. Barbosa MC assisted with the statistical analysis and with the final manuscript drafting.

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