INTRODUCTION

We have used low-dose prednisone, in conjunction with granulocyte, colony-stimulating factor (G-CSF), and erythropoietin, to treat an elderly patient with higher-risk myelodysplastic syndrome (MDS). Our findings indicate that such treatment is safe and may be effective in the long-term survival of such patients with minimal side effects.

Myelodysplastic syndromes (MDS) are a diverse group of hematological disorders that affect the blood and bone marrow. Different types of medications have been tried in MDS; however, no effective treatment has yet been established. Currently, most patients with higher-risk MDS are treated with low-intensity regimens that are based on hypomethylating agents (HMAs) such as 5-azacitidine or decitabine. However, these chemotherapeutic agents are not free of toxicity. Across azacitidine and decitabine studies, approximately 50% of patients develop Common Toxicity Criteria (CTC) grade 3 or 4 cytopenias, particularly during the first treatment cycle, necessitating intensive transfusion support, close monitoring, and placing patients at increased risk of febrile neutropenia episodes.

We have treated a newly diagnosed elderly patient with higher-risk MDS with a combination of granulocyte-colony-stimulating factor (G-CSF), low-dose prednisone, and recombinant erythropoietin (EPO). The rationale of such treatment was that this combination may induce differentiation of the immature, myeloid, and erythroid precursor cells, inhibit proliferation of the blast cells, and potentially increase or stabilize the platelet count. Another logic behind this protocol was that this treatment may also improve the circulating neutrophil count, prevent serious infections, and avoid the undesirable effects of chemotherapy, thus improving the quality of life.

Our patient continued to demonstrate positive and satisfactory results 14 months after the therapy was started. The patient went into and remained in stable, continuous partial remission. His circulating neutrophil count...
increased and was generally within normal limits, while the hemoglobin level is maintained at ~8 g/dl without a need for blood transfusion. The platelet count has remained low (~40,000/µl) but was stable and required no platelet transfusions. Occasional minor elevations of the neutrophil count (up to 15,000/µl) were treated with diminished allocations of G-CSF. The peripheral blood smears continued to show a small number (1%–4%) of blasts and blast-like cells and morphologic features of myelodysplasia in all three cell lines. The patient’s response was slow, to begin with, but had been sustained over an extended period of time. Unfortunately, he contracted Covid-19 infection and died 10 days later, despite adequate treatment, including Covid-19 protocol, which involved dexamethasone, remdesivir, and convalescent plasma.

2 | CASE REPORT

The patient, a 75-year-old white male patient with a past medical history significant for hypertension, chronic obstructive pulmonary disease, and hyperlipidemia, was brought to the emergency room (ER) with a history of syncopal attack. On physical examination, the patient was noted to be anemic, but he was not in acute distress. There was no jaundice, cyanosis, or edema. His abdomen was soft and non-tender. Bowel sounds were heard. The liver, spleen, and kidneys were not palpable. There was no palpable lymphadenopathy. Heart sounds S1 and S2 were identifiable, along with a soft ejection systolic murmur. The chest was clear to auscultation. His vital signs were stable—blood pressure 125/70 mm Hg, pulse 72 pm; respiration 18 pm, and temperature 97.6°F.

Laboratory investigations revealed WBC 0.9 × 10⁹/L, hemoglobin 8.9 g/dl with normal MCV, and MCH, and a platelet count of 92 × 10⁹/L. A manual differential count of his peripheral blood smear revealed 47.0% neutrophils, 46.0% lymphocytes, 1% bands, 2% monocytes, 1% basophils, 1% blasts (Figure 1A), and 2% blast-like cells (Figure 1B). There were 10 nucleated RBCs per 100 WBC (Figure 1C). The peripheral blood smear revealed hypogranularity and hypolobation (pseudo-Pelger-Huet anomaly) of neutrophils (Figure 1D), multinuclear (Figure 1E) and bizarre nuclear forms (Figure 1F). Red cells showed marked anisocytosis, poikilocytosis, dimorphic picture, presence of ovalocytes and macro-ovalocytes (Figure 2), and marked basophilic stippling (Figure 2 inset). The peripheral blood smear also displayed platelet anisocytosis and giant platelets (Figure 2). His serum iron level was normal at 70 μg/
dl (normal range 45–182), the total iron-binding capacity was normal at 374 μg (normal range 261–478) and the percent saturation was slightly low at 19% (normal range 20–50). His reticulocyte count was raised at 7.5% (normal range 0.5%–1.5%). The LDH was raised at 405 (normal range 105–210 U/L). His B12 (390 pg/ml) and folic acid (15.0 ng/ml) levels were also within normal limits. His erythropoietin level was 26 mU/ml (normal range 4–26 mU/ml). His complete metabolic profile was mostly normal, except for total bilirubin, which was slightly increased at 2.3 mg/dl (normal range 0.3–1.0 mg/dl) and glucose was slightly raised at 151 mg/dl (normal range 74–100 mg/dl). The routine urine analysis was negative.

Because of severe neutropenia, low hemoglobin level, and abnormal cytologic findings in the peripheral blood smear, hematological malignancy was suspected and the patient was admitted for further evaluation, diagnosis, and management. Soon after his admission to the hospital, the patient underwent a bone marrow examination, which revealed a slightly hypercellular (~60%) bone marrow (Figure 3) with an increased number of blast cells (12%; Figure 4) and marked dysplastic changes in all three cell lineages (Figures 5-7). There was marked basophilic stippling, but no ring sideroblasts were seen. The bone marrow biopsy section revealed focal clusters of immature myeloid precursor cells (Figure 8).

Flow cytometry studies of the peripheral blood sample revealed an increased blast cell population of 2% of the events. The blast population was positive for dim CD45, CD34, CD117, and HLA-DR, while negative for CD13, CD33, CD14, and CD15. The immunophenotype was compatible with a myeloblast. The granulocytes were slightly decreased and consisted mostly of mature-appearing granulocytes. No clonal B-cell or atypical T-cell population was detected.

Flow cytometry studies of the bone marrow aspirate sample revealed an increased population of cells that were positive for dim CD45, CD34, CD117, and HLA-DR, while negative for CD13, CD33, CD14, and CD15. The immunophenotype was compatible with a myeloblast. The granulocytes were slightly decreased and consisted mostly of mature-appearing granulocytes. No clonal B-cell or atypical T-cell population was detected (Figure 9).

Cytogenetic analysis of a 24-h unstimulated bone marrow culture demonstrated an abnormal male karyotype. Of the 20 mitoses analyzed, one was normal and 19 showed an abnormal karyotype with an extra chromosome (trisomy 8; Figure 10). FISH analysis was positive for trisomy 8 but negative for RUNX1/RUNX1T1, CBFB/MYH11, BCR/ABL, MECOM, KMT2A rearrangement, and MONOSOMY 5 (DELETION OF 5Q), MONOSOMY 7 (DELETION OF 7Q), MONOSOMY 20 (DELETION OF 20Q). The patient was diagnosed with acute myeloid leukemia (AML) with trisomy 8 and monosomy 20.
Molecular studies for FLT3, IDH1, IDH2, and TP53 were negative. The patient was diagnosed to have high-risk MDS, which was determined by the age, cytopenias, percentage of blasts in the marrow, and abnormal cytogenetic profile (trisomy 8).

Because of the patient's age (75 years) and a diagnosis of MDS with an excess of blasts, cytogenetic abnormality, and the degree of peripheral blood cytopenia, the patient was considered at higher risk (IPSS-R score 3). The patient was referred to hospice care. However, the patient's family declined this option and requested a treatment that did not involve chemotherapy. At this point, the patient was started on low-dose prednisone 20 mg orally daily, G-CSF (filgrastim) 300 μg subcutaneously three times a week (Monday, Wednesday, and Friday), and epoetin (Procrit) 30,000 units subcutaneously once a week. The patient did not receive any other cytokines or chemotherapy. Prednisone was gradually tapered and was reduced to 5 mg orally daily for the last 6 months, G-CSF was reduced to 300 μg once a week, and epoetin was reduced to 30,000 units once every 2 weeks for the last 4 months.

Within 2 weeks of the start of the cited treatment, his circulating neutrophil count began to increase. The hemoglobin concentration and platelet count remained low (Hb –8 g/dl, platelet –40–60,000/μl) but stable and did not

**FIGURE 6** Bone marrow aspirate smear showing dysplastic changes in granuloid precursors. (A)- pseudo Pelger-Huet anomaly, (B)- bizarre nuclei, (C)- a giant metamyelocyte

**FIGURE 7** Dysmegakaryopoiesis: multinuclear megakaryocytes, top row - bone marrow aspirate smear. Bottom row: mono, bi, and multi-nucleated megakaryocytes—bone marrow biopsy section

**FIGURE 8** Bone marrow biopsy section demonstrating focal clusters of immature myeloid precursors (blast cells) which can be easily identified by the presence of nucleolus and nucleoli. Two cells in mitosis (arrows) can be seen
require RBC or platelet transfusion. The peripheral blood smear continued to show a small number (2%-4%) of blast and blast-like cells but no overt signs of leukemic transformation. As stated earlier the patient contracted Covid-19 infection and expired soon thereafter.

3 | DISCUSSION

The ideal therapeutic approach for older (age ≥65 years) patients with MDS, particularly higher-risk groups of patients, is not known. Although allogeneic hematopoietic stem-cell transplantation can induce long-term remission in patients with MDS, such therapy is not applicable for most patients, since the median age at diagnosis usually exceeds 70 years as is in the case under discussion. Challenges facing current standard-of-care therapies for higher-risk MDS include poor overall survival,
limited duration of response, and singular mechanistic action.\textsuperscript{3,11,12} Responses achieved with currently available treatment are often less than 1 year of duration,\textsuperscript{11} and these therapies focus on either decreasing leukemic proliferation or limiting immune activation.\textsuperscript{11,13} Many higher-risk MDS patients require repeated blood transfusions and are often at risk for serious infections and hospitalization.

In general, higher-risk elderly patients are treated with demethylating agents such as 5-azacitidine or decitabine since the publication of an article that demonstrated treatment with demethylating agent results in superior remission rates, as compared with supportive care, and in some cases a delay in blastic transformation.\textsuperscript{14} In a recent randomized study that compared azacitidine treatment with conventional care in patients with high-risk disease, the median survival was 24.5 months in the azacitidine group, as compared with 15.0 months in the conventional care group.\textsuperscript{15} However, treatment for elderly patients with high-risk MDS with demethylating agents is not free of toxicity and treatment-related mortality can be quite high.\textsuperscript{3,4,15} Furthermore, once a drug fails the prognosis is poor in these patients. Further treatment options are limited and median survival is less than 6 months.\textsuperscript{16,17}

Myelodysplastic syndrome has been considered a malignant condition and consequently treatment of this condition has been chemotherapy, except for a few studies where G-CSF and erythropoietin were tried in patients with low-risk disease and minimal transfusion-dependence.\textsuperscript{18,19} We took a different approach, believing that perhaps this condition is a manifestation of an underlying disorder\textsuperscript{20} rather than a malignant condition. Accordingly, we treated our patient not with chemotherapy but with a combination of prednisone, and myeloid and erythroid-stimulating factors such as G-CSF and EPO. We believe this is the first reported higher-risk MDS patient who was treated in this combination. It achieved excellent results. We believe this observation merits further evaluation and a prospective trial. However, as we have reported earlier,\textsuperscript{20} the diagnosis of MDS is not uniform and considerable variations exist among the MDS patients as well as diagnosticians. And that is why perhaps individual disease courses vary highly and treatment approaches need to be tailored to symptom burden, risk of progression to AML, and comorbidities.\textsuperscript{12} HMA therapy is approved only for IPSS higher-risk MDS patients in Europe but they are approved for the treatment of all patients with MDS in the US.\textsuperscript{21} The National Comprehensive Cancer Network (NCCN) is recommending HMA use primarily for patients with intermediate or high-risk MDS who are not candidates for intensive therapy, who are unlikely to respond to other treatment modalities or as a bridge to allo-stem-cell transplantation.\textsuperscript{22}

This disease is often misclassified as evidenced by the fact that over 50% of patients in certain registries were considered “MDS—unclassifiable”.\textsuperscript{10,23} When bone marrow biopsies are not studied in parallel with bone marrow aspiration during the investigation and diagnosis of MDS, the abnormal localization of blast cells may be missed and as a result, high-grade MDS may be misdiagnosed as low or intermediate risk thus jeopardizing the correct stratification of this disease and thereby influencing the prognostic outcome. As a result, one has to be mindful of comparing apples and oranges in the setting of the same or similar treatment.

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**CONFLICTS OF INTEREST**

The author declares no conflict of interest.

**AUTHOR CONTRIBUTIONS**

The author conceptualized the study and wrote the manuscript.

**DATA AVAILABILITY STATEMENT**

Data available on request from the authors.

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