

Managing myelodysplastic syndromes in very old patients: a teaching case report

Pasquale Niscola
Massimiliano Palombi
Malgorzata Monika
Trawinska
Andrea Tendas
Marco Giovannini
Laura Scaramucci
Alessio Perrotti
Paolo de Fabritiis

Hematology Unit, Sant'Eugenio
Hospital, Rome, Italy

Abstract: The introduction of hypomethylating agents in the treatment of myelodysplastic syndromes (MDS) has significantly changed the clinical scenario of these diseases, which afflict predominantly older individuals. However, some concerns regarding the optimal application of these innovative and costly agents in the treatment of geriatric high-risk MDS remain. We report here the case of a nonagenarian treated with hypomethylating agents achieving a long-lasting clinical response and a significant improvement in her functional status. Our case confirmed that functional status and biological status, rather than the chronological age alone, can substantially guide the plan of an appropriate treatment strategy in high-risk MDS patients; moreover, the current case emphasizes the need for targeted studies in the field of geriatric MDS in order to formulate guidelines on the appropriate use of these costly agents, so that candidate patients can receive adequate treatment to preserve their quality of life and life expectancy, but at the same time avoiding unnecessary costs deriving from the use of high-cost drugs for those in whom a significant therapeutic result cannot be reasonably expected.

Keywords: myelodysplastic syndromes, azacitidine, older patients

Introduction

Myelodysplastic syndromes (MDS), with an incidence rate of four to five new cases per 100,000 population per year,¹ a median age of about 70 years,^{1,2} and mainly chronic course, are frequently managed in clinical practice by a hematologist. The majority of individuals with MDS are of older age, frail, and often afflicted by several comorbidities;² only a minority of patients are suitable for potentially curative approaches, such as intensive chemotherapy and stem cell transplantation.^{1,3,4}

Recently, low-dose chemotherapy and targeted agents, such as lenalidomide and azacitidine,^{1,4} have been adopted with favorable results in groups of patients with MDS. The introduction of hypomethylating agents in the treatment of MDS has significantly changed the clinical scenario of this disease.^{4,5} However, some concerns regarding the optimal application of these innovative and costly agents⁶ in the treatment of geriatric MDS remain.

In light of our recent experience in this setting, we report herein the case of a very old patient with MDS whom we have followed for the last 3 years. The present case provides, in our opinion, some interesting discussion points in regards to the diagnosis, management, and treatment of MDS in elderly patients.

Correspondence: Pasquale Niscola
Hematology Division, San Eugenio
Hospital, Piazzale dell'Umanesimo
10, 00144 Rome, Italy
Tel +39 06 5100 3241
Fax +39 06 5100 2390
Email pniscola@gmail.com

Case report

The patient was a 91-year-old woman kept under our care because of peripheral blood (PB) trilinear pancytopenia. The patient underwent routine tests, which excluded medical illnesses, infectious diseases, and other secondary conditions of altered blood counts, such as deficiency disorders, tumors, bleeding, and so on. A bone marrow (BM) examination was not initially performed given the patient's very advanced age and her unwillingness to submit to the diagnostic procedure. The morphological analysis of the PB smear showed anisopoikilocytosis of erythrocytes and platelets, along with hypogranularity and nuclear hyposegmentation of granulocytes; no circulating immature cells were found. These findings were suggestive of an MDS framework and the patient was regularly followed up.

However, the patient experienced worsening cytopenia; the patient had an ever increasing transfusion requirement of packed red blood cells and platelet concentrates. Given the difficulty of traveling to our treatment facility so frequently to receive transfusion support, the patient was followed at her home by our specialized team of hematological home care.⁷ During the following months, the patient was cared for at her home with increased transfusion requirement, persistent thrombocytopenia (platelet count around 1000/ μ L) with platelet transfusion refractoriness, and episodes of mucocutaneous bleeding. In other respects, the patient was well and did not have significant comorbidities; in addition, despite the disturbances related to cytopenia, she maintained an active life and a satisfactory personal independence in activities of daily living in her own home (Barthel⁸ and Katz⁹ indexes were 60% and 4/6, respectively), with the support and presence of her loved ones.

About 2 years after the diagnosis of suspected MDS, with the patient being almost 94 years old, a BM was performed. The morphological analysis of the BM smear showed a marked trilinear dysplasia with 15% blasts. Cytogenetic analysis showed a normal karyotype. Thus, the MDS was classified as intermediate grade 2 and intermediate risk according to International Prognostic Scoring System (IPSS)¹⁰ and World Health Organization adapted Prognostic Scoring System (WPSS),¹¹ respectively. A full reassessment of the general conditions made it possible to highlight the lack of relevant comorbidities or complications of the underlying disease; the MDS-specific comorbidity index¹² score was 0.

After a frank discussion with the patient and her family, 5-azacytidine (75 mg/m², schedule 5 + 2 + 2)¹³ was offered. The patient was properly informed and gave her consent. The treatment was administered on an outpatient basis,

whereas the transfusion support was given at home.⁸ The therapy was well tolerated and the cytopenia gradually improved until near-normalization of PB counts and complete transfusion independence, which were achieved after the third course of 5-azacitidine. To date, six courses of 5-azacitidine have been administered and a BM aspirate showed an absence of blast cells, although BM dysplastic features persisted; her hemogram is near-normal. We plan to continue the treatment as long as it remains effective and well tolerated.

Conclusion

Our experience outlined some concerns and decisions that hematologists encounter daily in managing elderly MDS patients, especially in light of the availability of new drugs that can alter the course of the disease. In fact, the clinical scenario of MDS has changed in the last few years from a treatment approach limited to symptom control and disease-related clinical complications to the possibility of achieving significantly long-lasting hematological responses,^{14–16} survival benefits,^{17–21} and improvement in quality of life²⁰ by novel agents. It has been reported that treatment with 5-azacitidine provides significantly better therapeutic results than other traditional treatments; 5-azacitidine has firmly established a standard of care. The use of 5-azacitidine in our case suggests three main discussion points.

First, if MDS is suspected, should it be fully diagnosed in very elderly patients? MDS diagnosis can be ruled out only through BM examination, but performing BM aspiration can be painful and carries a small risk of adverse events; thus, it is often avoided or postponed.²² It is important to note that if MDS worsens and leads to acute myeloid leukemia progression, postponing BM examination may result in the loss of the useful therapeutic window for the administration of new drugs such as hypomethylating agents. Thus, in our opinion, the point remains open to the discussion.

Second, should very elderly MDS patients be treated? Although the financial cost of hypomethylating agents is substantial, it should be weighed against the patient's potential benefits, in terms of improvement in clinical outcomes, quality of life, and transfusion requirements.⁶ Moreover, the therapeutic effects of hypomethylating agents are not related to patient age; indeed, favorable responses have been achieved in patients over 75 years of age,¹⁵ such as in our patient. The IPSS¹⁰ and WPSS¹¹ have an established role in treatment decision making; however, other important aspects, such as the presence of comorbid illnesses and functional status impairment (extremely frequent in very elderly individuals) should be taken into account.^{4,5}

Consequently, in very old MDS patients, the identification of patients who may benefit from hypomethylating agents may be a concern. Once again, this question remains unanswered; however, we hope that future studies could, and should, clarify this matter of crucial importance.

Third, where should very elderly MDS patients be treated? The application of supportive care measures has critical value in preserving the quality of life and functional performance of these patients;^{4,5} in this regard, our case illustrated the significant role that specialized home care service can play in the management of MDS patients.^{7,21} Indeed, elderly patients are frail and their access to the hospital may be difficult due to several factors: complex and severe symptom burden, the impairment of daily living activities, social isolation, financial issues, and psychological limitations. Thus, in our opinion, the best setting in which to manage elderly patients with MDS is home care; however, a specialized home care team, networking with the hospital and the other local services, is required for adequate management of these complex patients at home.

In conclusion, to the best of our knowledge, we have reported on the oldest MDS patient treated with 5-azacitidine. In light of our experience, we would like to emphasize the need for targeted studies in the field of geriatric MDS in order to formulate guidelines on the appropriate use of costly new drugs, such as hypomethylating agents, in order to ensure adequate treatment to preserve patients' quality of life and life expectancy, but at the same time avoiding unnecessary costs associated with the use of high-cost drugs for those in whom a real benefit cannot be reasonably expected.

Disclosure

The authors have no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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