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Myelodysplastic Syndromes in the Elderly –  
A Prominent Medical Concern with Significant Effects on Healthcare Systems

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Abstract

Myelodysplastic syndromes (MDS) represent one of the most challenging health-related problems in the elderly. As the population continues to age, MDS will become a more prominent medical problem with a significant effect on healthcare systems. MDS are characterised by dysplastic morphology in the bone marrow in association with ineffective haematopoiesis; there are various pathophysiological causes of these diseases, including genetic abnormalities within myeloid progenitors, altered epigenetics and changes in the bone marrow microenvironment.

There is uncertainty about how to diagnose patients who may benefit from a specific treatment; in fact, MDS probably constitute several molecularly distinct entities that share common changes in blood and bone marrow. The International Prognostic Scoring System (IPSS) is a useful tool to guide treatment decisions, but revisions of the original IPSS are under way as it fails to consider many aspects of the treatment of MDS patients, especially in elderly patients. This article examines treatment goals, options and directions when treating elderly MDS patients.

Furthermore, it explores how treatment has evolved according to new survival data and how various therapies are contributing to improve the survival rate.

Keywords

Elderly, myelodysplastic syndromes, novel agents, supportive care, treatment strategies

Disclosure: This work was supported by the Italian Association for Cancer Research (AIRC), Milan.

Acknowledgement: The authors would like to thank C Perillo for the English edit of the manuscript.

Received: 1 July 2010 Accepted: 30 July 2010 Citation: European Oncology, 2010,6(2):70-4 DOI: 10.17925/EOH.2010.06.02.70

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The primary myelodysplastic syndromes (MDS) are one of five major categories of myeloid neoplasms.1 Their actual incidence is unknown, but it has been suggested that it may be higher than estimated.7 Ageing is an important risk factor for the development of these diseases; in fact, the majority of patients with MDS are >55 years of age.1 Recent data4 indicate that 86% of MDS cases are diagnosed in individuals >60 years of age and the percentage tends to increase significantly with age.3,4

Patients with MDS usually present with anaemia and other cytopenias as well as bone marrow dysplasia that involves at least 10% of the myeloid cells.2 Haematopoietic progenitors in MDS show a decreased capacity of differentiation and an increased tendency for apoptosis leading to ineffective haematopoiesis. Over time, many patients develop an increase in bone marrow blasts and about 30% develop acute myeloid leukaemia (AML).2 The clinical variation of MDS presentation ranges from indolent to life-threatening. Up to 10% of patients with MDS experience serious bleeding, including haematuria and gastrointestinal, retinal and central nervous system haemorrhage. Patients may develop Sweet’s syndrome (5–10%), splenomegaly (10–20%), hepatomegaly (5–26%) and lymph-node enlargement (5–15%).

A risk-adapted approach to therapy has been adopted4 in decision-making. The most commonly used prognostic tool in the evaluation of patients with an MDS is the International Prognostic Scoring System (IPSS) (see Table 1),7 which was consequently modified by a World Health Organization (WHO) classification.39 Other proposed variables include age, performance status, bone marrow fibrosis, new cytogenetic risk categories, thrombocytopenia, serum levels of lactate dehydrogenase and β2-microglobulin, immunophenotypes of myeloid progenitor cells and, recently, gene-methylation signatures.11-17

Myelodysplastic Syndromes in the Elderly Population

Difficulties of admittance to treatment, co-morbidity, social environment and cognitive status and the large variation in performance and functional status are critical points to be taken into consideration in the elderly MDS population, together with the biological and clinical properties of MDS.4 In this context, one paradigmatic example is the management of anaemia; in fact, in elderly patients it has been demonstrated that even a mild reduction in the haemoglobin level or mild anaemia leads to a significant increase – nearly double the risk – of all-cause mortality.30 Furthermore, it is stated that mortality is a major concern and those patients with anaemia also experience a significant impact on their activity level, which not only affects their quality of life but also may have significant economic consequences. In fact, in those individuals who have a reduction in haemoglobin, one of the major complaints is
fatigue or inability to carry out what they normally previously performed with the same vigour and energy. Everyday activities such as shopping may be restricted due to anaemia and therefore these patients have a significant reduction in their quality of life. Anaemia has also been associated with a reduction of cognitive function. Accordingly, decision-making about treatment is extremely complex and geriatric factors need to be incorporated into prognostic scoring for MDS.

Recently, Goldberg et al. reported data from the Medicare Standard Analytic Files of 1,394,343 65-year-old individuals. Interestingly, most patients with MDS diagnosed during the first quarter of 2003 suffered from cardiac-related events during the three-year follow-up. Significant increases in prevalence of diabetes, dyspnoea, hepatic diseases and infections were also reported in MDS patients compared with the overall Medicare population. Patients with MDS requiring red blood cell (RBC) transfusions had greater prevalence of these co-morbidities. AML developed within three years in 9.6% of the population, with increased transformation among those patients who received a transfusion. The three-year Kaplan-Meier age-adjusted survival for MDS was 60%, which was significantly lower than in the Medicare population, and mortality was further increased among transfused MDS patients.

Management of Lower-risk Myelodysplastic Syndrome Patients

The ‘watch and wait’ approach is generally recommended for a patient with a low or intermediate risk of MDS, a haemoglobin level >10g/dl and platelet counts of 50,000–100,000/μl without the need for transfusion. These patients may be able to maintain their usual activity levels without therapy. Regular check-ups are important because there is a risk of progression to more severe forms of MDS or AML.

However, in most cases treatment of MDS patients with lower-risk disease generally requires management of the patient’s symptomatic anaemia with its related fatigue. RBC transfusion support is the community standard of care for this hypoprolifereic anaemia with associated ineffective erythropoiesis. Initiation of transfusion therapy should be based on clinical evaluation of anaemia-related symptoms and co-morbid illness rather than on a defined haemoglobin level, especially because optimal haemoglobin levels have not been defined for the elderly population.

In clinical practice, pre-transfusion haemoglobin levels in MDS are generally maintained between 8 and 10g/dl, but all quality-of-life studies show significantly greater fatigue and dyspnoea in MDS patients than in healthy controls, and it is not known whether a more liberal transfusion strategy can improve quality of life or outcome. However, due to the potential complications of chronic transfusions (iron overload, negative impact on patient’s daily schedules), treatment to improve anaemia has been of central importance.

Organ accumulation of non-transferrin-bound iron in MDS patients can result in oxidative cellular injury and clinical sequelae, including cardiac and hepatic dysfunction, pancreatic endocrine insufficiency with glucose intolerance, arthropathy, impotence and fatigue. Chelation therapy is the cornerstone of supportive therapy to reduce iron accumulation and the potential for organ complications. Evaluation of chelation treatment is recommended when serum ferritin levels reach 2,500μg/l. Three chelating agents are in use worldwide: deferoxamine, which is administered parenterally, and deferasirox and deferiprone, which are oral chelating agents. Oral administration improves compliance, especially in elderly patients, and can minimise the personnel, time, cost of equipment and supplies necessary for parenteral drug administration.

Chelation in transfusion-dependent MDS patients induces a significant decrement of serum ferritin after 12 months of therapy. Reversible elevation in serum creatinine occurred in 25% of patients. Moreover, in patients who received standard chelation therapy after transfusions, the median overall survival from the time of diagnosis was better than in non-chelated patients (115 versus 51 months). After stratification by prognostic variables, including IPSS category, age, sex and transfusion requirements, the survival difference favouring the chelated group remained significant. More in-depth studies are required to determine the survival benefit, cost feasibility and the right moment to begin therapy.

### Table 1: International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Factor</th>
<th>Notes</th>
<th>Value</th>
<th>IPSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts</td>
<td>≤5%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–10%</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11–20%</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21–30%</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Normal: -Y only, Sq- only or 20q- only</td>
<td>good</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abnormalities other than good or poor</td>
<td>Intermediate</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Complex: 3 or more abnormalities or abnormal chromosome 7</td>
<td>Poor</td>
<td>1.0</td>
</tr>
<tr>
<td>Cytopenaia</td>
<td>Haemoglobin &lt;10g/μl, ANC &lt;1,500μl, platelet count &lt;100,000/μl, each counts as a value of 1</td>
<td>0/1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

The numerical scores for the blast per cent, the cytogenetic changes and the cytopenaia are combined to give the total numerical score.

The scores equal a risk category:

- Low
- Intermediate 1
- Intermediate 2
- High

The risk categories are sometimes combined as:

- Low and intermediate 1 = low-risk MDS
- Intermediate 2 and high = high-risk MDS

Total Score | IPSS Risk Category | Examples
---|-------------------|------------------
0 | Low | A total score of 0 (low risk):
0.5–1.0 | Intermediate 1 | Marrow blasts ≤5%
1.5–2.0 | Intermediate 2 | No cytogenetic abnormalities
≥2.5 | High | Haemoglobin <10g/dl with normal platelet counts and normal neutrophil counts

A total score of 2.0 (intermediate 2):

- 5–10% blasts
- Deletion of chromosome 7
- Anaemia and a platelet count of <50,000/μl

ANC = absolute neutrophil count; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes.
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For patients lacking del(5q) but with relatively low serum erythropoietin (EPO) levels, treatment with erythroid-stimulating agents (ESAs) should be initiated. Treatment with ESAs, when given in adequate doses (e.g. recombinant human EPO 40,000–60,000 units subcutaneously [SC] once to twice a week, or darbepoietin 300mg SC every 1–2 weeks), has been associated with erythroid response rates of approximately 20–40%. Responses with ESAs are generally noted within one to two months, if they are to occur.

In general, those patients with relatively low serum EPO levels and whose RBC transfusion need was <2 units per month had a 70% chance of responding, whereas in those with neither of these features the response rate was <10%; those with one feature had a 23% response rate. Lower-risk patients have higher response rates than those with higher-risk disease. Given the existing body of evidence that suggests relative safety with ESAs in MDS, cautious use of ESAs continues to be appropriate. The use of these drugs to raise the haemoglobin level high enough to avoid RBC transfusion, along with a change in the target haemoglobin level, is advisable.

Patients with severe neutropenia or thrombocytopenia also require supportive management. The depth of these cytopenias relates to both marrow blast counts and IPSS category, and thus are more common in higher-risk disease.

Myeloid cytokines, such as granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF), have been functional in increasing neutrophil levels in MDS patients. Although the data have indicated good long-term tolerance of G-CSF, they have not indicated clinical benefit with the prophylactic use of these agents, thus they are generally reserved for neutropenic patients with resistant or recurrent infections or following chemotherapy-induced febrile neutropenia.

The prevalence of thrombocytopenia (<100x10^9/l) in MDS ranges from 33 to 76%. Severe thrombocytopenia is generally managed with platelet transfusion support. Recent phase II clinical trials have demonstrated the efficacy of the thrombopoietic compound romiplostim for increasing platelet levels and decreasing thrombocytopenic adverse events either alone or in combination with hypomethylating agents.

For lower-risk anaemic patients with del(5q) cytogenetic abnormalities, the data have indicated very high erythroid response rates (66%) with good durability of response (median two years) to lenalidomide. Partial or complete cytogenetic responses occurred in 73 and 45% of patients, respectively, and were found in those with del(5q) alone or with those additional abnormalities. Thus, lenalidomide treatment as front-line therapy is recommended for the management of these patients. However, as yet there are limited data indicating improved overall survival with long-term lenalidomide therapy.

An advantage of using this agent to treat elderly patients with MDS is that it is an oral agent that can be easily managed in the outpatient setting. Patients need careful monitoring of blood counts and supportive transfusion, but they do not need to come to the physician’s clinic to receive infusional therapy and do not need any inpatient monitoring.

For lower-risk patients lacking del(5q) but with high serum EPO levels, therapy is mainly based on features associated with relatively high response rates to immunosuppressive therapy (IST), i.e. antithymocyte globulin (ATG). These clinical features include younger age (i.e. <60 years), lower-risk disease, marrow hypopcellularity, human leukocyte antigen DR 15 (HLA DR15) histocompatibility type, evidence for a paroxysmal nocturnal haemoglobinuria clone and shorter disease duration. Of these variables, younger age and marrow hypopcellularity appear to be the most useful predictors of IST response in lower-risk patients. For patients lacking features indicative of good response to IST, the use of hypomethylating agents should be considered. Recent pilot studies from the National Institutes of Health (NIH) group demonstrated the utility of alemtuzumab (anti-CD52 antibody) in this setting.

Management of Higher-risk Myelodysplastic Syndrome Patients

For higher-risk MDS patients, the primary goals of treatment involve extending overall survival and altering the course of the disease by delaying the time to AML transformation. Other treatment objectives include improving quality of life, providing symptom control and supportive care and achieving transfusion independence. Appropriate management of this challenging patient population requires a multidisciplinary approach that includes close monitoring by a physician, frequent laboratory tests and cautious use of transfusions in order to improve quality of life and provide symptomatic relief.

Complete response (CR) has been considered a required surrogate for improved survival in acute leukemias. This method of measurement has traditionally been considered critical for survival improvement in MDS as well; however, no study has demonstrated an association between CR achievement and extended survival. A recently published randomised trial of azacitidine (S-AZA) versus conventional care has raised questions about the requirement of CR for improved survival in MDS.

High-dose chemotherapy followed by allogeneic haematopoietic stem cell transplantation (HSCT) is currently the only known potentially curative treatment for MDS, but it is rarely taken into consideration in the elderly population. The outcomes of allogeneic transplant vary with age, patient co-morbidities, disease status, type of induction regimen and donor. This strategy has not been tested in controlled trials. In general, according to the most recent data, it is suggested that for high-risk patients transplant at diagnosis maximises average survival. However, no net years of life were lost for patients with lower-risk IPSS MDS if transplant was delayed until disease progression.

Reduced-intensity conditioning (RIC) has been developed to extend allogeneic stem cell transplantation to older patient populations and patients with co-morbidities. Because RIC does not administer myeloablative conditioning, the success of the transplants requires a robust graft-versus-leukaemia effect. While short-term mortality is certainly decreased using these approaches, the incidence of chronic graft-versus-host disease is substantial, and two-year mortality may approach that of myeloablative stem cell conditioning. While allogeneic transplant with RIC represents an important treatment option, particularly for older patients with MDS, its optimal application has yet to be determined.
DNA MTIs deplete nuclear DNA methyltransferase and promote the synthesis of DNA in a process that results in the methylation marks from the parent DNA strand being ‘erased’. DNA MTIs are now considered the first-line agents in the treatment of MDS, and both 5-AZA and decitabine (DEC) have demonstrated haematological improvement compared with best supportive care (BSC). In addition, 5-AZA showed a significant overall survival benefit over a combined cohort of three conventional-care regimens. Because the 5-AZA nucleosides must be incorporated into DNA in order to effect methylation reversal, higher concentrations of these agents may sabotage this effect through cell-cycle inhibition. A biphasic dose–response curve for the relationship between methylation reversal and DEC nucleoside concentration has been demonstrated in vitro.

The majority of patients who responded to 5-AZA treatment (75%) achieved improvement by the fourth cycle, with time to any response occurring with a median number of three cycles. The total response increased to 90% by the sixth cycle. Therefore, it is important to continue the treatment with a DNA MTI for several cycles before concluding that the patient will not develop a haematological response. In patients receiving transfusions at baseline, 80% of 5-AZA patients became transfusion-independent. In addition, quality-of-life components, such as fatigue, physical functioning, dyspnoea, psychosocial distress and positive effect, significantly improved in patients treated with 5-AZA compared with BSC. In this trial, overall survival favoured 5-AZA treatment (20 versus 14 months), although this trend was not statistically significant. This was most likely attributable to the cross-over design.

The most significant data for DNA MTI therapy emerged from an international randomised trial with 5-AZA. In this trial, after a median follow up of 21.1 months the 5-AZA group had a significantly longer median survival time of 24.5 months versus 15 months for the conventional-care group. Median time to progression of AML was also significantly decreased in 5-AZA patients compared with those receiving conventional care (17.8 versus 11.5 months). 5-AZA patients also had significantly higher rates of any haematological response (29 versus 12%), CR (17 versus 8%), partial response (PR) (12 versus 4%) and any haematological improvement (49 versus 29%) compared with those receiving conventional care.

This significant prolongation in survival in patients treated with 5-AZA, despite a modest CR rate, demonstrates that achieving a CR is no longer a sufficient predictor of a therapy’s ability to extend survival and alter the course of MDS and chronic myelomonocytic leukaemia (CMML). DEC is another DNA MTI that has been studied predominantly in higher-risk MDS patients. Similar to 5-AZA, the most commonly studied dose schedule (15mg/m² intravenously) for DEC was derived empirically rather than through careful dose-finding studies. These studies indicate that while dose schedule of DEC is active in MDS as well as 5-AZA, survival has not been improved when compared with BSC as for the second one.

While the haematological response rates to both 5-AZA and DEC nucleosides are similar, the survival advantage demonstrated by the dose schedule of 5-AZA compared with conventional care, as well as the absence of such a survival advantage in response to the dose schedule of DEC in two randomised studies, makes 5-AZA the drug of choice for 5-AZA nucleoside-naïve high-risk MDS patients.

Patients in the intermediate 2 and high-risk IPSS categories may require treatment with the same type of chemotherapy that is used for AML (cytarabine, daunorubicin, idarubicin, mitoxantrone, thalidomide). Planning this form of treatment also takes into account the patient’s age and any co-existing medical conditions.

The drugs may be given alone or in combinations of two or three agents. In some cases, low dosages are used. Initially, chemotherapy will make the patient’s blood cell count worse. This means that the doctor has to assess the benefits of intensive chemotherapy and consider both the severity of disease and the chance that the patient will respond to the chemotherapy with remission.

### Current Clinical Trials in Myelodysplastic Syndromes

Several clinical trials are studying treatments with combinations of US Food and Drug Administration (FDA)-approved drugs, such as 5-AZA or DEC, and AML-type chemotherapy.

Agents work in different ways to kill cancer cells so the combined use of these in therapy may kill more MDS cells, or may be as effective as standard MDS therapies, but with less toxic side effects.

Current trials are considering:

- the effectiveness of arsenic trioxide in combination with 5-AZA or with tipifarnib, a farnesyl transferase inhibitor, and gemtuzumab ozogamicin;
- whether the duration of response improves with 5-AZA maintenance for patients who achieve a CR or PR after intensive chemotherapy;
- the effectiveness of clofarabine in combination with AML-type chemotherapy;
- the effect of lonafarnib and tipifarnib on transfusion independence for patients who receive between one and eight platelet transfusions every four weeks; and
- the effectiveness of valproic acid in combination with DEC; and the effectiveness of vorinostat in combination with 5-AZA.

### Conclusions

Many complex variables should be considered in elderly MDS patients. To make management decisions in older MDS patients, the first step must be integrating geriatric and oncology nursing to allow an individualised approach to this unique population. All the above-mentioned factors influence the potential inability of the older
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patient to tolerate certain intensive forms of therapy. The multiple medical problems that affect the older population and the use of related medications to manage them must also be considered.

Particularly important in the elderly MDS patient is the evaluation of the age-related decline in normal bone marrow function, including diminished capacity for response to stressors such as infections or myelosuppressive treatments.

Further observation may be useful to determine whether the patient has an indolent or progressive course, and to evaluate whether the MDS presents as isolated but persistent mild anaemia or as a more progressive and aggressive anaemia state that accumulates excess blasts in the marrow and leads to fatal AML. Therefore, patients may be categorised by age, co-morbidities and by stable versus unstable disease before suggesting specific treatment approaches.

To improve access to treatment, emphasis must be placed on oral therapies that can be easily administered in the outpatient setting with growth-factor support to minimize the requirements of transfusions. Intensive efforts are required to find strategies that keep elderly patients functional and in their homes during treatment, minimising time in hospital.

Careful evaluation of functional status, the ability to tolerate treatment, the effects of disease progression and general overall health can provide the best opportunity for support of older patients, considering that palliative and supportive care represent care companion to maximising quality of life.