

News in MDS

Clin Geriatr Med. 2016 Feb;32(1):155-73. doi: 10.1016/j.cger.2015.08.010.

Myelodysplastic Syndromes and Acute Myeloid Leukemia in the Elderly.

Klepin HD¹.

Abstract

Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are hematologic diseases that frequently affect older adults. Treatment is challenging. Management of older adults with MDS and AML needs to be individualized, accounting for both the heterogeneity of disease biology and patient characteristics, which can influence life expectancy and treatment tolerance. Clinical trials accounting for the heterogeneity of tumor biology and physiologic changes of aging are needed to define optimal standards of care. This article highlights key evidence related to the management of older adults with MDS and AML and highlights future directions for research.

News in MDS

Eur J Haematol. 2015 Nov 27. doi: 10.1111/ejh.12709. [Epub ahead of print]

Efficacy and safety of a 5-day regimen of azacitidine for patients with high-risk myelodysplastic syndromes.

Fujimaki K¹, Miyashita K¹, Kawasaki R¹, Tomita N².

Abstract

Although a 7-day regimen of azacitidine (AZA) is the standard treatment of high-risk myelodysplastic syndromes (MDS), AZA is difficult to administer during weekends in an outpatient setting. We retrospectively investigated the outcome of a 5-day regimen of AZA in patients with high-risk MDS. High-risk MDS was defined as MDS with intermediate 2- or high-risk MDS according to the International Prognostic Scoring System. Every month AZA was given at 75 mg/m² per day for 5 - 7 days in hospital for first cycle and 5 days in outpatient for second cycle and later. Between April 2011 and December 2013, AZA treatment was initiated in 25 patients (men, 22; women, 3; median age, 75 years; age range, 59-86 years). The median number of AZA cycles was 10 (range, 1-24). 20 patients received more than 3 cycles of AZA and 13 (52%) achieved any hematological improvement (HI). The median time to first response was 2 cycles (1-3). The most common non-hematological adverse events were neutropenia in 21 patients and thrombocytopenia in 17 patients. Nineteen patients died. The main cause of death was disease progression (5 patients) and infectious complications (11 patients). The median overall survival was 13.2 months. The 5-day AZA regimen showed a good continuation rate of more than 3 cycles and an equivalent HI with the 7-day regimen.

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News in MDS

Expert Opin Ther Targets. 2015 Nov 26. [Epub ahead of print]

Inositide-dependent Signaling Pathways as New Therapeutic Targets in Myelodysplastic Syndromes.

Mongiorgi S¹, Finelli C², Yang YR³, Clissa C^{2,4}, McCubrey JA⁵, Billi AM¹, Manzoli L¹, Suh PG³, Cocco L¹, Follo MY¹.

Abstract

INTRODUCTION:

Nuclear inositide signaling pathways specifically regulate cell proliferation and differentiation. Interestingly, the modulation of nuclear inositides in hematological malignancies can differentially affect erythropoiesis or myelopoiesis. This is particularly important in patients with Myelodysplastic Syndromes (MDS), who show both defective erythroid and myeloid differentiation, as well as an increased risk of evolution into Acute Myeloid Leukemia (AML). Areas covered: This review focuses on the structure and function of specific nuclear inositide enzymes, whose impairment could be linked with disease pathogenesis and cancer. The authors, stemming from literature and published data, discuss and describe the role of nuclear inositides, focusing on specific enzymes and demonstrating that targeting these molecules could be important to develop innovative therapeutic approaches, with particular reference to MDS treatment. Expert opinion: Demethylating therapy, alone or in combination with other drugs, is the most common and current therapy for MDS patients. Nuclear inositide signaling molecules have been demonstrated to be important in hematopoietic differentiation and are promising new targets for developing a personalized MDS therapy. Indeed, these enzymes can be ideal targets for drug design and their modulation can have several important downstream effects to regulate MDS pathogenesis and prevent MDS progression to AML.

News in MDS

Nat Commun. 2015 Nov 26;6:8806. doi: 10.1038/ncomms9806.

Whole-exome and targeted sequencing identify ROBO1 and ROBO2 mutations as progression-related drivers in myelodysplastic syndromes.

Xu F¹, Wu LY¹, Chang CK¹, He Q¹, Zhang Z¹, Liu L¹, Shi WH¹, Guo J¹, Zhu Y¹, Zhao YS¹, Gu SC¹, Fei CM¹, Wu D¹, Zhou LY¹, Su JY¹, Song LX¹, Xiao C¹, Li X¹.

Abstract

The progressive mechanism underlying myelodysplastic syndrome remains unknown. Here we identify ROBO1 and ROBO2 as novel progression-related somatic mutations using whole-exome and targeted sequencing in 6 of 16 (37.5%) paired MDS patients with disease progression. Further deep sequencing detects 20 (10.4%) patients with ROBO mutations in a cohort of 193 MDS patients. In addition, copy number loss and loss of heterogeneity (LOH) of ROBO1 and ROBO2 are frequently observed in patients with progression or carrying ROBO mutations. In in vitro experiments, overexpression of ROBO1 or

ROBO2 produces anti-proliferative and pro-apoptotic effects in leukaemia cells. However, this effect was lost in ROBO mutants and ROBO-SLIT2 signalling is impaired. Multivariate analysis shows that ROBO mutations are independent factors for predicting poor survival. These findings demonstrate a novel contribution of ROBO mutations to the pathogenesis of MDS and highlight a key role for ROBO-SLIT2 signalling in MDS disease progression.

News in MDS

Gan To Kagaku Ryoho. 2015 Nov;42(11):1443-6.

[Unidentified Inflammatory Disease Induced by Azacitidine Therapy for Myelodysplastic Syndrome].

[Article in Japanese]

Inagaki S¹, Tamai Y, Yoshizawa M, Sato S, Kanbe E, Tanaka E.

Abstract

We report a 73-year-old woman with myelodysplastic syndromes(MDS)of the refractory anemia with excess of blasts-1 subtype, which was diagnosed in April 2014 on the basis of cytopenia for two cell types. After completing 3cycles of azacitidine(AZA)therapy, the patient was admitted to our hospital based on an initial presentation of high fever. During hospitalization, the high fever and increasing inflammatory reaction persisted. We reevaluated the effect of MDS in this patient and concluded that the AZA administration was successful and the MDS was extremely stable. On medical examination and inspection, the patient had an unidentified inflammatory disease. First, we treated her with high-dose steroid pulse therapy. However, the effect of the treatment was transient. Furthermore, the effects of cyclosporin A and oral steroid therapy were poor; therefore, we initiated tocilizumab administration. Nevertheless, she died of multiorgan failure. An increasing serum IL- 6 level induced by the AZA therapy was later confirmed. Recent studies have reported the immunomodulatory effects stimulated by AZA therapy in MDS. This case is a valuable reminder that an unidentified inflammatory disease can be induced in the course of AZA therapy for MDS.

News in MDS

Leuk Res. 2015 Jul;39(7):679-83. doi:10.1016/j.leukres.2015.04.001.Epub 2015 Apr 15

Change of prognosis of patients with myelodysplastic syndromes during the last 30 years.

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Abstract

During the last years, more and more treatment modalities are available for MDS patients. Therefore, we were interested if this is reflected in an improvement of the outcome of the patients. We analyzed the survival and rate of leukemic progression of 4147 patients from the Duesseldorf MDS registry diagnosed during the last 30 years and found an improvement of survival in those patients diagnosed after 2002 (30 vs. 23 months, $p < 0.0001$). In detail, the improvement of the prognosis was restricted to high-risk MDS patients diagnosed between 2002 and 2014 in comparison to the patient group diagnosed between 1982 and 2001 (19 vs. 13 months, $p < 0.001$), whereas the prognosis of low-risk MDS patients did not change significantly. The improvement of survival was still measurable after exclusion of RAEB-t patients and of those, that received an allogeneic stem cell transplantation. In line with this finding, we found a lower AML progression rate in the later diagnosed group. Unfortunately, we could not identify a clear reason for this finding but rather a multifactorial cause should be assumed. As death due to bleeding complications and infections was significantly lower, an improvement of BSC may be one of the underlying causes.

News in MDS

Leuk Res. 2015 Oct;39(10):1028-33. doi: 10.1016/j.leukres.2015.06.008. Epub 2015 Jun 20.

Updated recommendations on the management of gastrointestinal disturbances during iron chelation therapy with Deferasirox in transfusion dependent patients with myelodysplastic syndrome - Emphasis on optimized dosing schedules and new formulations.

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Abstract

Myelodysplastic syndromes (MDS) are oligoclonal hematopoietic disorders characterized by peripheral cytopenias with anemias being the most prevalent feature. The majority of patients will depend on regular transfusions of packed red blood cells (PRBC) during the course of the disease. Particularly patients with MDS and low risk for transformation into acute myeloid leukemia and low risk of early death will receive PRBC transfusions on a regular basis, which puts them at high risk for transfusional iron overload. Transfusion dependence has been associated with negative impact on organ function and reduced life expectancy. Recently, several retrospective but also some prospective studies have indicated, that transfusion dependent patients with MDS might benefit from consequent iron chelation with regard to morbidity and mortality. However, low treatment adherence due to adverse events mainly gastrointestinal in nature is an important obstacle in achieving sufficient iron chelation in MDS patients. Here, we will summarize and discuss the existing data on Deferasirox in low risk MDS published so far and provide recommendations for optimal management of gastrointestinal adverse events during iron chelation aiming at improving treatment compliance and, hence, sufficiently removing excess iron from the patients.

News in MDS

Letter to the Editor

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Clonal architecture of del(5q) myelodysplastic syndromes: aberrant CD5 or CD7 expression within the myeloid progenitor compartment defines a subset with high clonal burden

OPEN

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Myelodysplastic syndromes (MDSs) represent a heterogeneous hematopoietic stem cell disorder.¹ A precise estimation of the prognosis within the various MDS subgroups is essential for tailored therapeutic decisions. Especially, MDS patients with an isolated deletion of the long arm of chromosome 5 (del(5q)) represent a distinct subgroup regarding clinical outcome with a favorable prognosis in the majority of cases.² Furthermore, they present with characteristic cytomorphological features, such as hypolobated megakaryocytes, macrocytic anemia and a normal or increased peripheral platelet count.³ Recently, flow cytometry (FCM) has been shown to serve as a valuable additional diagnostic and prognostic tool, especially to separate between unilineage and multilineage dysplasia.^{4, 5} Besides, it is known that abnormal antigen expression on myeloid progenitor cells (myPCs) is associated with a poor outcome.^{6, 7} In fact, aberrant CD7 expression on myPC of anemic lower-risk MDS patients predicts for a significantly lower response rate to erythropoiesis-stimulating agent (ESA) therapy irrespective of comparable other clinical predictive markers (erythropoietin level, transfusion burden).⁸ The pathophysiological background for this observation is still unknown. Notably, it has not been shown so far whether these distinct immunophenotypic characteristics correlate with presence and extent of clonal hematopoiesis, which in turn might not be responsive to growth factor stimulation. Therefore, in this study we separated different hematopoietic cell compartments of del(5q) MDS patients by fluorescence-activated cell sorting (FACS) and quantified the respective distribution of clonal burden with interphase fluorescence in situ hybridization (iFISH).

News in MDS

Eur J Haematol. 2015 Sep 5. doi: 10.1111/ejh.12679. [Epub ahead of print]

Response to erythropoietic-stimulating agents in patients with chronic myelomonocytic leukemia.

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Abstract

BACKGROUND:

The efficacy of erythropoietic-stimulating agents (ESA) in chronic myelomonocytic leukemia (CMML) is unknown. Our objective was to analyze erythroid response (ER) and overall survival (OS) in a series of 94 patients with CMML treated with ESA.

METHODS:

We analyzed a series of 94 patients with CMML treated with ESA included in the Spanish and Düsseldorf-MDS registries.

FINDINGS:

ER was observed in 64% of patients and red blood cell (RBC) transfusion independence in 31%. The median duration of ER was 7 months (range, 0-88). CPSS and EPO level were significantly associated with ER in multivariate analysis ($P = 0.003$). Considering only patients with CPSS low- or intermediate-1-risk group, the absence of RBC transfusion dependence and erythropoietin (EPO) level predicted ER ($P = 0.003$ and $P = 0.008$, respectively). In multivariate analysis, only the EPO level retained its prognostic value ($P = 0.029$). Achievement of ER correlated with a better survival since ER evaluation ($P = 0.016$).

INTERPRETATION:

The CPSS and EPO levels are adequate tools to select CMML patients with symptomatic anemia who may benefit from treatment with ESA. A significant ER to ESA is expected in anemic patients with low/intermediate-1 CMML risk by the CPSS and a low endogenous serum EPO level.