

Congress Report

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The 10th International Symposium on myelodysplastic syndromes (MDS) was held in Patras, Greece, 6–9 May 2009. Progress in understanding the pathogenesis of and treatment of MDS and advances in its treatment were discussed during oral and poster sessions.

Update on MDS classification

“The availability of new treatment options has brought a new impetus to ensuring MDS patients are diagnosed and classified appropriately,” said Professor John Bennett, chairman of the MDS Foundation in his lecture on the recently updated WHO MDS classification system.

Speaking to the audience in the first of two diagnosis and prognosis sessions, Professor Bennett, who is also Emeritus Professor of Medicine at the University of Rochester Medical Center in the USA, said: “The last decade has witnessed the emergence of several therapeutic options for patients with myelodysplastic syndromes. Objective criteria for diagnosis, proper classification and risk stratification are more important than ever before.”

Professor Bennett presented details of last year’s WHO update to the 1997 version of the MDS

classification system. Citing 11 key changes (Box 1), he noted that, for the first time, the WHO system now proposes a diagnosis of “presumptive MDS” in cases with persistent clinical cytopenias without dysplasia if certain cytogenetic abnormalities are present. He concluded: “There is a clear need for a standardised way to diagnose MDS and classify it, a need for minimally required diagnostic criteria and more objective criteria.”

Proposals for revised IPSS component

A new validated database could form the basis of a revised cytogenetic component in the forthcoming reassessment of the MDS International Prognostic Scoring System (IPSS), according to Professor Detlef Haase from Georg-August University in Goettingen, Germany.

Professor Haase presented details from the merging of three large

databases. Based on 2664 patients, the merging of the German-Austrian MDS Registry, the Spanish MDS Registry and the IMRAW-group registry produced data comparable to each individual database. Cytogenetic subgroups were then divided into four prognostic groups: favourable, intermediate-1, intermediate-2 and unfavourable, according to the definitions below. The original cytogenetic component of the IPSS was based on just 816 patients and consisted of three subgroups.

Based on the expanded database, median survival for each group was 51 months, 29 months, 15.6 months and 5.9 months, respectively. Extending median survival is a management objective that is feasible with new treatment options. Professor Haase added that the median time to 25% AML transformation was 71.9 months, 16 months, 6 months and 2.8 months, respectively. Differences in median survival and AML transformation rates ($p < 0.0001$) were highly significant between each pair of subgroups. The cytogenetic subgroups were verified by univariate and multivariate analyses.

Definition of prognostic subgroups:

- *Favourable* (5q-, 12p-, 20q-, +21, -Y, 11q-, t(11)(q23), normal, 2

Box 1: Changes under the revised WHO classification system

- Refractory cytopenia with unilineage dysplasia (RCUD) includes cases in which dysplasia is demonstrated in $\geq 10\%$ of cells in the affected cell line. Patients have unicytopenia or bicytopenia. Refractory anaemia, refractory neutropenia (RN) and refractory thrombocytopenia (RT) under this category. RN and RT previously classified as MDS unclassified.
- MDS associated with isolated del (5q) is a category for patients with unilineage erythroid dysplasia, isolated del (5q) and less than 5% blasts. Term 5q-syndrome less emphasised as lenalidomide benefit is the same for patients with 5q syndrome or isolated del (5q).
- MDS unclassified includes patients with pancytopenia and unilineage dysplasia. Patients with no overt dysplasia but cytogenetic evidence of MDS. RCUD and RCMD cases in which bone marrow blasts are less than 5% and peripheral blasts are 1%.
- Refractory cytopenia of childhood has been proposed
- RAEB-1 now includes cases with 5–9% bone marrow blasts and 2–4% peripheral blood blasts. No Auer rods present.
- RAEB-2 includes cases with 10–19% bone marrow blasts and 5–19% peripheral blood blasts. Auer rods presence regardless of blast % = RAEB-2 or CMML-2 classification.
- Most cases of MDS with myelofibrosis are RAEB cases.
- CMML diagnostic requirements remain the same.
- Atypical CML is renamed atypical CML, BCR/ABL negative to emphasise the importance of obtaining tests.
- RARS-T as an entity is proposed.
- Up to 60% of patients have the JAK2 V617F mutation.
- Myeloproliferative disorders is replaced by myeloproliferative neoplasms



abnormalities including 5q-)

- *Intermediate-1* (+1q, 3q21/q26-abnormalities, +8, t(7q), +19, -21, any other single, any other double)
- *Intermediate-2* (-X, -7/7q-, 2 abnormalities including -7/7q-, complex = abnormalities)
- *Unfavourable* (complex >3 abnormalities)

Value of continued therapy with azacitidine

THE hypomethylating agent azacitidine can reduce transfusion dependence and nearly doubles the 2 year overall survival rate from 26% to 51%,¹ with data suggesting that continued exposure to the drug is important, according to a review of azacitidine data in a session on optimising epigenetic therapies.

Presenting the review, Professor Lewis Silverman of the Mount Sinai School of Medicine in New York, said: "achievement of a complete response is not an obligatory endpoint" for improved survival as demonstrated by results of the AZA-001 trial.¹

The AZA-001 trial demonstrated that azacitidine (AZA) was the first treatment to extend overall survival (OS) in higher-risk MDS patients significantly. Professor Silverman told the congress that the current treatment paradigm, which assumes a direct relationship between complete remission (CR) and survival, is questionable, as results from AZA-001 showed that CR was not necessary to prolong OS. Although the CR rate in AZA-001 was modest (17%), while the partial remission (PR) rate of 12% and

haematologic improvement (HI) rate of 49% were also predictive of prolonged survival, he explained.

Professor Silverman also presented details of an analysis he led to assess the median number of AZA treatment cycles associated with the achievement of first response and of best response in patients with higher-risk MDS. Of the 179 AZA-treated patients, 91 (51%) achieved a CR, PR or HI. For those 91 patients, a median number of three treatment cycles were needed to achieve their first response. More than three-quarters (81%) of patients achieved a first response by six cycles, and 90% achieved a first response by nine cycles. For 57% of responders (n=52), their first response was their best response. But nearly half of respondents (43%) achieved an improved response with additional treatment cycles. Commenting on this data, first presented at ASH 2008², Professor Silverman said that "continued dosing with azacitidine could further improve patient responses".

Future therapies for MDS

Prospective treatments could improve the outlook for patients with MDS. Currently under investigation are treatments that could improve haematopoiesis in lower risk patients and disease-modifying strategies for patients with higher risk disease who did not have success with hypomethylating agents. Professor Alan List from the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, suggested that the biological complexity of MDS indicated that such future agents will complement existing therapies and provide a foundation for novel combinations.

According to Professor List: "The range of agents competing to address the issue of improving haematopoiesis in lower risk patients and strategies for higher risk patients who have failed to respond on existing therapies have never been greater." Candidates waiting in the wings include a vast array of small molecules affecting

biological response signals, classical antineoplastics, the addition of histone deacetylase inhibitors to azacitidine and lenalidomide, clofarabine combined with decitabine and other inhibitors of DNA methylation. A range of traditional cytotoxics are also under investigation. Professor List said that investigational strategies for higher risk disease, including agents targeting survival signals such as PIM-1 kinase, PI3 kinase-delta, mTOR, scr/lyn kinase, the Cdc7 DNA replication regulator, EphA3 RTK, Cdc25C and cyclin-D1 suggested greater therapeutic options in the future for patients with higher risk MDS.

Age substantial barrier to iron chelation therapy

The first analysis of a European survey of physicians' management of iron overload in MDS patients has suggested that age and life expectancy are the most substantial barriers to initiating chelation therapy.

Results from the MDS Iron-overload Detection Insight Survey (MIDIS) – led by Professor Pierre Fenaux from Hôpital Avicenne/ Université Paris – also showed that only 27% of transfusion-dependent patients were treated with iron chelation therapy.

The results, the data cut-off for this first analysis was 10 March 2009, were based on 219 physicians from 27 countries. Most respondents were haematologists (69%). There were polarized views on some of the other barriers to iron chelation therapy. One in four physicians said that a reduction in the patient's quality of life was a strong barrier to initiating iron chelation therapy but the same number said that quality of life did not influence iron chelation therapy. Table 1 details a selection of triggers that 'led' or 'very much led' to physicians initiating iron chelation therapy. Professor Fenaux⁵ said: "Further efforts are needed to educate physicians about the consequences of not treating iron overload, even in more elderly patients and to raise awareness about their

Table 1. Triggers that 'led' or 'very much led' to physicians initiating iron chelation therapy

Trigger	n (%)
Serum ferritin level of >1000 ng/mL	163 (74)
Candidate for allogeneic stem-cell transplantation	162 (74)
Patient is aged 55–64 years	160 (73)
Need to prevent organ dysfunction and complication	155 (71)
Transfusion requirement of >2RBC units per month	148 (68)
Low, Int-1 or RA, RARS, 5q-MDS	141 (64)
Lifetime transfusions of >20 RBC units	139 (63)
Convenience of oral chelation therapy	138 (63)
Rapid rise in serum ferritin level	119 (54)
Patient is aged 65–74 years	116 (53)
Knowledge gathered in training sessions and congresses	111 (51)
Patient life expectancy is >1 year	110 (50)

right to iron chelation therapy as well as to other treatments."

Further recruitment into the MIDIS study, which was initiated at ASH 2008, is ongoing. The study is run by the MDS Foundation and the European School of Haematology (ESH).

Transfusion independence with azacitidine treatment

The AZA-001 trial showed that azacitidine prolonged overall survival in higher-risk MDS. A retrospective analysis of this trial and a previous trial presented at the conference showed that about half of azacitidine-treated patients achieved transfusion independence.

The analysis⁶ of patients treated with azacitidine in the AZA-001 study⁷ and the CALGB 9221 study⁸ showed that patients receiving azacitidine achieved transfusion independence at comparable rates.

The team led by Professor Lewis Silverman from the Mount Sinai School of Medicine in New York evaluated the consistency of azacitidine's ability to induce red blood cell (RBC) and platelet transfusion independence in baseline-dependent patients. At baseline or crossover in CALGB 9221 and baseline in AZA-001, 67% and 62% of AZA patients were RBC transfusion-dependent, respectively, and 19% and 21% were platelet transfusion-dependent. In

CALGB 9221, patients' FAB subtype did not influence the likelihood of transfusion independence and independence rates for all FAB subtypes and higher-risk groups were similar to those for patients with higher-risk MDS in AZA-001. Patients in CALGB 9221 who crossed over to AZA also had high rates of transfusion independence (see Table 2). Professor Silverman said: "These results indicate the consistent beneficial effects on erythropoiesis and thrombopoiesis with azacitidine treatment."

Real-world data show benefit of hypomethylating agents in the elderly

Data from a German MDS Register showed that elderly patients treated with hypomethylating agents received a substantial survival benefit in line with benefits demonstrated in clinical trials. The results underscore the need to treat elderly patients with therapies above and beyond supportive care.

Results from the Dusseldorf Registry, based on 44 patients with a median age of 70 years, showed that median survival time after treatment with either azacitidine or decitabine was 28 months.⁹

By contrast, median survival for patients treated with best supportive care was just 10 months ($p=0.00026$). Median survival times for patients treated with either low-dose Ara-C-treated patients or induction chemotherapy were 20 and 21



months, respectively. Survival times for both of these conventional treatments were inferior to hypomethylating agents. Study investigators said that their data provides further support to arguments to treat with epigenetic drugs, even for patients fit for intensive chemotherapy. Study leader Dr Andrea Kuendgen from Heinrich-Heine University in Dusseldorf, said: "In our opinion, hypomethylating agents should be considered the treatment of choice in elderly high-risk MDS patients who are not candidates for allografting."

Professor Valeria Santini from the University of Florence discussed survival times for elderly patients with MDS who were treated with azacitidine. She noted that the AZA-001 trial had demonstrated that MDS patients aged >75 years treated with azacitidine had a significantly longer overall survival than patients treated with best supportive care. Professor Santini then presented new research based on 36 elderly patients with MDS who were treated at her centre, showing that their median overall survival was comparable to that obtained in the AZA-001 trial (20.5 months versus 25.6 months, respectively).¹⁰ Median overall survival did not differ significantly between patients <75 years and those >75 years ($p>0.7$). Professor Santini said: "These results confirm that azacitidine is safe and effective in very elderly MDS patients." Haematological and non-haematological adverse events were mostly mild and uniformly distributed in the patient population, independently of age, she added.

Table 2. RBC and platelet transfusion-dependent patients who achieved TI during AZA treatment

	AZA-001 n/ N ^a (%) (95% CI) Higher risk ^b		CALGB 9921 n/N ^a (%) (95% CI)		
	AZA	AZA ^c	All FAB subtypes		Higher-risk ^b
			AZA after BSC ^d	AZA ^c	AZA after BSC ^d
RBC	50/111 (45%) [36, 55]	29/65 (45%) [32, 58]	21/40 (53%) [36, 69]	21/48 (44%) [30, 59]	13/24 (54%) [33, 74]
Platelets	16/38 (42%) [26, 59]	8/15 (53%) [27, 97]	9/13 (69%) [39, 91]	7/14 (50%) [23, 77]	5/8 (63%) [25, 92]

^a n = number of patients who achieved TI; N = number of patients RBC- or platelet-dependent at baseline.

^b RAEB, RAEB-1, CMML, AML.

^c Randomized to AZA.

^d Randomized to BSC then crossed-over to AZA upon disease progression.



New data confirms good survival for MDS del(5q) patients

The median overall survival of patients with MDS and del(5q) is 5 years, new data from the prize-winning study of the congress shows.

The multicentre study of 241 patients with MDS and del(5q), led by Professor Germing of Heinrich-Heine University in Germany, showed that survival of these patients was high and comparable to patients with refractory cytopenia with unilineage dysplasia (RCUD) and refractory anaemia with ring sideroblasts (RARS). The patients, median age 67, were followed from first diagnosis and received only best supportive care. Those patients with a low risk IPSS had a median survival of 67 months, and patients in the intermediate-1 risk group had a median survival of 37 months (p=0.0023). Patients with MDS and del(5q) as a sole chromosomal aberration had a better outcome than patients with additional aberrations (63 months versus 37 months). But MDS and del(5q) was associated with a risk of AML-transformation similar to RCMD without del(5q). Of the 241 patients, 47 (19.5%) progressed to AML (>20% medullary blasts). The factors associated with the risk of AML transformation were intermediate-1 IPSS risk group, elevated marrow blast count and transfusion need at

diagnosis. There were no differences in survival and progression rate between the participating centres, said Professor Germing. "Further cytogenetic and molecular studies are warranted to identify patients at greater risk of progression," added Professor Germing.

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Pilot study shows value of hypomethylating therapy education

A French pilot study of a leaflet about MDS and options for treatment with hypomethylating agents suggests that such an educational tool can reduce therapy-related anxiety amongst patients.¹¹

The four-page leaflet, intended for patients, their families and healthcare providers, included information on MDS subtypes and prognosis. It also detailed the azacitidine's mechanism of action, mode of administration and expected adverse events. Developed with input from a group of patients and their families, the leaflet was evaluated via a questionnaire by a separate group of 15 patients and their relatives. More than 90% of patients reported that the leaflet was clear and adequate and that it had a favourable impact on therapy-related anxiety.

