appears that heme-oxygenase-1 plays the role of Dr. Jekyll by increasing red cell life span in circulation and also plays the part of Mr. Hyde by decreasing bone marrow erythropoiesis.

The work of Fraser *et al.* represents an important step in our understanding of the complex interplay between erythroid and macrophage biology in the regulation of red cell production and destruction. In particular, it brings to our attention the previously unsuspected and distinct roles of heme-oxygenase-1 in murine erythroid biology through its action on macrophages. However, many questions remain. How does heme-oxygenase-1 deficiency account for the observed microcytosis and decreased hemoglobin content of red cells? Is there perturbation of iron homeostasis due to dysregulation of hepcidin production?[12] Importantly, do the reported findings using the murine system account for the hematologic phenotype noted in the very rare cases of human heme-oxygenase-1 deficiency?[13,14]

What then are the implications of these current findings? One is that heme-oxygenase-1 may play a much broader role in erythroid biology than previously suspected and likely plays a role in a number of human red cell disorders. A second implication is that there is clearly a complex interplay of cell-cell interactions in regulating various biological functions. Finally, the work of Fraser *et al.* gives us a valuable impetus to further explore the complex role of macrophages in various aspects of erythroid biology.

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Personalized medicine in myelodysplastic syndromes: wishful thinking or already clinical reality?

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General concepts of managing patients with myelodysplastic syndromes

This editorial will start with the important (and true) premise that the term myelodysplastic syndromes (MDS) covers a group of heterogeneous and complex hematologic disorders primarily found within the older population. In fact, its diversity makes the disease challenging and "truly personalized", not only in terms of diagnostics but also in carrying out clinical decision-making. The heterogeneity of MDS manifests in the individual patient as a disease ranging from an indolent condition with a considerable life expectancy to forms approaching the aggressiveness of acute myeloid leukemia (AML). A risk-adapted treatment strategy is, therefore, mandatory for a disease showing such a highly variable clinical course. Prognostic factors may be subdivided into those related to the patient's general characteristics and health condition and those related to the MDS disease itself. During the past 15 years, treatment has been stratified according to the International Prognostic Scoring System (IPSS) risk score; i.e. into "lower-risk" MDS (low/int-1, LR-MDS), where correction of cytopenia was the main objective, and "higher-risk" MDS (int-2/high, HR-MDS), where the reduction or delay of progression or AML evolution and prolonged survival was the objective. More recently, a revised version of the IPSS has been introduced (IPSS-R) subdividing patients into 5 risk groups with different outcomes in terms of AML evolution and survival. Using this new IPSS-R, one-quarter of LR-MDS per classical IPSS were re-classified as having a higher risk, and may potentially require more intensive treatment, while on the other hand a substantial subset of HR-MDS patients per classical IPSS were re-classified as lower risk suggesting that IPSS-R can refine the scoring of an individual MDS patient. Nevertheless, it is still a subject of controversy as to how

this score can be used to guide the treatment of MDS patients since currently available and licensed drugs have been developed based on the conventional IPSS.

Diagnostic workup of myelodysplastic syndromes: the first step towards a personalized risk-adapted therapeutic management

The diagnosis of MDS is a diagnosis of exclusion of other causes of cytopenia, especially in patients who do not present with an excess of blasts or who do not show any cytogenetic or molecular abnormalities. The emergence of innovative therapies that could alter the course of MDS has increased the options available for therapeutic management. However, it is essential that patients who could benefit from these treatments are accurately diagnosed as soon as possible after initial presentation. A morphological assessment and standard metaphase cytogenetics still remain crucial to the diagnosis of MDS,[1] while fluorescence *in situ* hybdrization (FISH) plays an important supplementary role, particularly in detecting specific abnormalities [e.g. del(5q)] in case of insufficient metaphases or of complex karyotype. Flow cytometry according to the European LeukemiaNet (ELN) guidelines[2] may prove to be a valuable tool in the diagnostic and prognostic evaluation of patients with MDS but is currently integrated into standard clinical practice only in some specialized centers. This comprehensive workup can potentially provide important predictive factors for a subsequent response to a given therapy [e.g. del(5q) and lenalidomide] in line with a "personalized approach" in MDS. Recently, developments in molecular technologies have led to major improvements in the understanding of the molecular pathogenesis of MDS, identifying somatic mutations in 80%-90% of MDS patients. These mutations, involving in particular genes encoding for splicing factors and epigenetic factors (Table 1), may help in the diagnosis of MDS in difficult cases (to confirm a clonal disease), although some of these mutations have recently been found at a lower frequency in healthy elderly individuals.[3] Furthermore, many of these newly discovered mutations (e.g. RUNX1, ASXL1, TP53) have an impact (mostly negative) on prognosis. They may thus allow for better stratification of patients within conventional scoring systems for different types of treatment. This is mainly the case for relatively young patients of intermediate prognosis using those systems, where presence of one or several unfavorable mutations may suggest more intensive treatment, including allogeneic hematopoietic stem cell transplantation (HSCT), being proposed. At the moment, this personalized approach (Table 2) is, however, not supported by prospective randomized trials.

Potential types of strategic management of myelodysplastic syndrome patients based on personalized medicine

'Watch and wait'

Personalized medicine in MDS can also mean that nothing other than supportive care is delivered because life expectancy is short due in particular to major comorbidities (Table 2). Fit patients with primary lower-risk MDS with asymptomatic cytopenia, absence of excess of blasts or poor-risk cytogenetics (and maybe no poor-risk molecular findings) do not need any treatment and should be followed regularly. Patients should be aware of the fact that the safe-

Table 1. Somatic mutations found in myelodysplastic syndromes according to frequency and clinical impact in patients treated with supportive care only.

Somatic mutations in myelodysplastic syndromes			
Function	**Mutation**	**Prognosis**	**Frequency**
Splicing	SF3B1	good	15-30%
	SRSF2	poor	5-10%
	U2AF1	poor	5-10%
	ZRSR2	neutral	5%
Methylation	DNMT3A	poor	5-10%
	TET2	neutral	15-25%
Methylation/ histone modifications	IDH1/ IDH2	mixed evidence	4-5%
Histone modification	ASXL1	poor	10-20%
	EZH2	poor	3-7%
Transcription factor	RUNX1	poor	5-10%
	TP53	poor	5-10%
	BCOR	poor	5-6%
	ETV6	poor	3%
Signal transduction	NRAS/KRAS	poor	5-10%

Table 2. Current clinical picture of "personalized medicine" in myelodysplastic syndromes.

Variable	Grading	Potential clinical consequence
Performance status	Good	Standard therapy including allogeneic HSCT
	Poor	Supportive care only
EPO level	Low	Treatment with ESA in case of anemia
	High	No treatment with ESA in case of anemia
Ferritin level	High	Treatment with iron chelation
Prognostic scoring systems (e.g. IPSS-R)	Good risk	Supportive care only
	Poor risk	Hypomethylating agents, allogeneic HSCT
Cytogenetics	Del(5q)	Targeted treatment with lenalidomide
Mutations	Good risk	Supportive care only
	Poor risk	- Standard therapy including allogeneic HSCT, - Intensified surveillance or early pre-emptive therapy in otherwise good-risk MDS (e.g. by IPSS-R)

HSCT: allogeneic hematopoietic stem cell transplantation; EPO: recombinant erythropoietin; ESA: erythropoiesis-stimulating agents; IPSS-R: revised international prognostic scoring system; MDS: myelodysplastic syndromes.

ty of this approach is dependent upon careful follow up. The goals of such subsequent follow up include the early recognition of worsening cytopenia, increasing number of circulating or bone marrow blasts, and cytogenetic as well as molecular evolution. In fact, this 'watch and wait' strategy might change in the future if improved prognostication (e.g. by molecular diagnostic tools) allow for a better identification of LR-MDS patients with a "higher-risk" profile based on genotype (e.g. mutation profile). Most importantly, a change in the current strategy will also require new and safe treatments capable of modifying the natural history of the disease.

Targeting anemia with erythropoiesis-stimulating agents

Treatment with ESAs [i.e. recombinant erythropoietin (EPO) or darbepoetin [DAR]) as single agent may induce erythroid responses in around 50% of unselected patients with LR-MDS. Although several trials, including phase III studies, have been performed with ESAs, and despite the fact that they are widely used and accepted in the medical community, still no specific ESA is currently licensed for the treatment of MDS. However, prospective trials are almost completed and results are awaited soon. Nevertheless, ESAs are considered a first-line treatment for patients with LR-MDS [mainly those without del(5q)] and anemia, provided they show pre-treatment variables predictive of response to treatment.[4] These include mainly a low (<500 U/L) endogenous EPO-level as well as low transfusion burden. When selecting patients according to this model, subsequent response rate can be easily predicted, thus omitting unnecessary treatment to patients: Weekly doses of 30,000-60,000 units of EPO, or 150-300 μg of DAR, yield an erythroid response rate of approximately 70% when the baseline EPO level is low and transfusion requirement absent or limited. Most responders to ESAs respond within 12 weeks of treatment and the median duration of response is approximately two years. Other predictive factors of response to ESA have been reported including the IPSS-R itself.[5] Immunophenotypic analysis of myeloid cells (aberrant immunophenotype being associated with ESA failure) or p-ERK1/2 expression (low expression being associated with ESA failure).[6,7]

Targeting anemia in genetically defined del(5q) myelodysplastic syndromes

Lenalidomide has been licensed recently in the EU for single del(5q) LR-MDS, with delays compared to the US due to concerns of induction of disease progression by the drug itself. Upon further analysis, disease progression appears not to be drug-related but rather a result of the great clinical heterogeneity of del(5q) MDS including the presence of a TP53 mutation in up to 20% of patients. Lenalidomide has shown high response rates predominantly in red blood cell transfusion dependent (RBC-TD) MDS patients with IPSS-defined low- or int-1 risk and del(5q).[8,9] In addition, lenalidomide has been shown to be active as a single agent even in patients with del(5q) HR-MDS,[10] although response rates are significantly lower compared to LR-MDS, which is likely a reflection of additional molecular events. Still, lenalidomide appears to specifically target myeloid clones with del(5q) that are haplo-insufficient for various genes located on this chromosomal segment, constituting in that sense a 'targeted drug'.

Recent data[11] demonstrated *TP53* mutations in a substantial proportion (approx. 20%) of MDS patients with IPSS low and int-1 disease and del(5q). Interestingly, patients with a *TP53* mutation are less likely to respond (absence of complete cytogenetic remission) to single agent lenalidomide.[12] Therefore, patients with a diagnosis of del(5q) LR-MDS harboring a *TP53* mutation should be considered a distinct (ìpersonalizedì) group requiring closer follow up and potentially intensified up-front treatment strategies, e.g. involving combinations of lenalidomide with hypomethylating agents (HMA) such as azacitidine within clinical trials.[13,14]

Targeting cytopenia and disease progression by demethylating therapies

Until recently, best supportive care (BSC) was considered the primary standard treatment for HR-MDS, except, for patients younger than 65-70 years of age[15] with a compatible donor, where allogeneic HSCT following myeloablative or non-myeloablative conditioning regimens was shown to be a curable option in many cases.[16] Recently, however, azacitidine and, to a lesser extent, decitabine have become the standard approach for older patients with higher-risk disease who are not amenable to allogeneic HSCT. Based on the randomized AZA001 study[17] comparing azacitidine with conventional care (mostly BSC and excluding allogeneic HSCT), the drug has become the approved standard therapy for HR-MDS patients. The label includes AML patients with 20%-30% blasts, thus also covering MDS RAEB-t patients according to the historic FAB classification. Notably, decitabine has also been approved for MDS (according to FAB classification, i.e. including RAEB-t) in the US, whereas in Europe, it is approved only for acute myeloid leukemia (AML) with at least 20% marrow blasts.

In the AZA001 trial, median overall survival was 24 months for patients treated with azacitidine compared to 15 months for patients who received conventional care. Importantly, not only patients who achieved complete or partial remission, but also those who had an improvement in cytopenias appeared to benefit from azacitidine treatment in terms of survival compared to a standard of care regimen. On the other hand, while hematologic response was seen independently of cytogenetic risk groups, including patients with complex abnormalities, poor-risk cytogenetic abnormalities were linked to lower survival rates compared to other cytogenetic abnormalities.[13] Predictive scoring systems for survival with azacitidine treatment based on conventional parameters, including RBC transfusion requirement, performance status, circulating blasts and karyotype, have been validated.[18] Recent data also suggest that a mutation profile (especially with TET2 gene mutations) may predict the success of therapy,[19] although this will have to be confirmed on larger series of patients.

Future outlook

Knowledge on the pathophysiology of MDS has greatly improved in the last few years with the advent of new genetic techniques. It is anticipated that the advent of new prognostic tools by mutation profiling analyses will further

improve the classification of the disease and will lead to therapeutic biomarkers. In fact, there is a clinical need to extend our current limited therapeutic portfolio by the detection of innovative therapeutic targets.[20] In the interest of our patients, we hope that these efforts will extend our therapeutic armamentarium in the near future and will offer truly personalized approaches.

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Aging and malignant hemopathies

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Aging was the theme of the 19th EHA Congress and a new scientific working group (SWG) was launched. Its first session was devoted to the increased incidence of malignant hemopathies in older patients. Three questions were addressed, and these are summarized below.

The role of immune senescence in the development of cancer

Aging is associated with the functional alteration of multiple organs, including our immune system, thus affecting immune surveillance, one of the major barriers that prevent the development of cancer. Throughout life, our body is exposed to numerous aggressions and challenges (e.g. infections, inflammation, free radicals, carcinogens, etc.), leading to a progressive waning in our immune defences.[1]

Immune cells involved in cancer protection work in close collaboration. The first line of defence involves the 'innate' immune system: dendritic cells, natural killer (NK) cells and macrophages. These cells can eliminate cancer cells by themselves, but with age, innate immunity is impaired by downregulation of macrophages, alteration in cytokine production, increased production of IL-10 by the increased number of myeloid-derived supressor cells (MDSC), and reduction of NK-cell cytotoxicity. Although the number of aging macrophages is usually normal, their functions [chemotaxis, phagocytosis, signal transduction, cytokine production, toll-like receptor (TLR) expression and function] are significantly reduced.[2] PGE 2 production by macrophages is increased[3] that may directly suppress T-cell functions. Phenotypic changes occur in NK cells leading to remodeling of NK-cell subsets: CD56 bright cells, a more