Recent frustration and innovation in myelodysplastic syndrome

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The definition of innovation and what it could mean for MDS

The term "innovation" in general means something completely original and more effective and, as a consequence, new, that "breaks into" a current system. In general terms, we would all agree that smartphones belong to recent innovations in human life. Concurrently, the field of hematology and oncology has been moving in a very dynamic fashion during the last decade. This is also true for myelodysplastic syndrome (MDS), but mainly in the field of pathophysiology and prognosis. In fact, since the introduction of azacitidine onto the market in 2009, there has been no registration of additional drugs for our patients with MDS. On the other hand, recent innovation in the MDS field involves a better understanding of how MDS might develop from an aging hematopoietic stem cell. This includes the characterization of the role and function of a complex network of molecular abnormalities which do not occur exclusively in MDS, but also in other hematological diseases. Herein, we intend to provide a short overview on recent innovations, but also on the challenges and frustrations within the field of MDS, especially regarding disease-specific therapies.

The new WHO classification

A morphological assessment of the blood and bone marrow and standard metaphase cytogenetics are still the standard of care in the diagnosis of MDS.[1] The current World Health Organization (WHO) defined criteria allow for a distinction between pure refractory anemia and refractory anemia with ringed sideroblasts, and patients with multi-lineage dysplasia and those with excess blasts of up to 20% in the bone marrow. Moreover, it transfers patients with an isolated deletion 5q into a separate category. This definition has been valuable as for the first time a genetic marker lesion also constituted a target for biological therapy (lenalidomide). A revision of the WHO classification has been recently published where some issues have been addressed.[2] This includes the fact that patients with MDS and del(5q) can harbor one additional abnormality (e.g. +8) apart from chromosome 7, because only the latter confers a poor prognosis in these patients. Additionally, the term "refractory anemia" will be abandoned and replaced with "MDS with single lineage dysplasia" (formerly RA/RARS/RT/RN) or "MDS with excess blasts" (formerly RAEB). This is because patients with MDS often have anemia, but not exclusively in the majority of cases where other lineages are affected. However, we believe and anticipate that the WHO classification will be amended in the near future because of the recent advances in molecular data.

Molecular markers and clonal hematopoiesis

In fact, important developments in molecular technologies have recently led to significant strides in the understanding of the potential molecular pathogenesis of MDS. Analyses of large non-MDS populations without cytopenias have even revealed that somatic mutations in hematopoietic cells can be acquired during a human lifetime, and are seen in >10% of people over 70 years of age.[3] The most frequently mutated genes are *DNMT3A*, *ASXL1* and *TET-2*, and those healthy individuals generally carry only one mutation. The presence of clonal hematopoiesis (in the absence of cytopenia) is associated with an increased risk of subsequent myeloid (MDS and AML) but also lymphoid malignancies, in addition to an increased mortality risk from several other causes (especially cardiovascular). However, most individuals with age-associated clonal hematopoiesis will never develop MDS. Therefore, this clinical state has been recently defined as "clonal hematopoiesis of indeterminate potential" (CHIP), but it is still unclear if it is analogous to monoclonal gammopathy of undetermined significance (MGUS) and clonal lymphocytes of unknown origin (CLUS),[4] because it does not only specifically increase the risk of one disorder, like MGUS or CLUS.

In proven MDS cases, most of the recently discovered mutations (e.g. *RUNX1*, *ASXL1*, *TP53*) have a negative impact on prognosis, while *SF3B1* has a positive impact on prognosis. Mutations may add prognostic value to existing scoring systems (IPSS, IPSS-R) for different types of treatment,[5] and may soon be incorporated into the revised IPSS (IPSS-R), thus forming the "IPSS-Rm". Nevertheless, the value of these molecular testing systems other than for diagnostic purposes (to confirm a suspected clonal disease) in daily practice, especially for treatment choice, remains debatable in the absence of large prospective studies.

Old and novel drugs and a European network on clinical trials (EMSCO)

Treatment with ESAs (i.e. recombinant erythropoietin (EPO) or darbepoetin) can induce erythroid responses in patients with lower-risk MDS (LR-MDS). Although several trials, including small phase III studies, have been performed with ESAs, and despite the fact that they are widely used and accepted in the medical community, as of yet no ESA is currently approved by health agencies (EMA, FDA) for the treatment of MDS. However, two prospective placebo-controlled randomized trials (*clinicaltrials.gov identifier: 01381809* and *clinicaltrials.gov identifier: 01362140*) have recently been completed and the results are expected soon. At least one of these studies may lead to the registration of this class of drugs. Nevertheless, response to an ESA is generally transient, and therapeutic options are needed for LR-MDS patients with anemia not responding to or relapsing after a response.

Lenalidomide is a potentially active drug in patients with non-del(5q) MDS, with erythroid responses seen in a quarter of unselected patients.[6] This phase II study by Raza *et al.* was the rationale to further investigate lenalidomide in non-del(5q) patients with anemia refractory to ESAs in a phase III placebo-controlled study.[7] Overall, 27% of patients treated with lenalidomide achieved transfusion independency ≥8 weeks compared with 2.5% of placebo-treated patients (P<0.001). The median duration of response was 8.2 months (range 5.2 to 17.8 months). The main adverse events were grade 3–4 neutropenia and thrombocytopenia, although the frequency of these events was lower in non-del(5q) patients (49.3% *vs.* 73.7% for neu-

tropenia and 37.3% *vs*. 64.2% for thrombocytopenia, respectively).[8] Recently, in a randomized trial, Toma *et al.* showed that in LR-MDS patients with ESA resistant anemia, the combination of LEN and EPO significantly improved erythroid response compared to LEN alone.[9]

Activin receptor inhibitors antagonizing TGFβ and SMAD signaling currently arise as promising targets to treat anemia in MDS patients. One of these emerging compounds is ACE 011 (sotatercept), an ActRIIA ligand trap consisting of the extracellular domain of hActRIIA linked to the $hIgG_1$ Fc domain. Originally, ACE 011 was developed to increase bone mineral density in bone diseases. Data from a phase II trial with ACE 011 in patients with anemia refractory to ESA and low- and and intermediate-1-risk MDS have shown considerable responses, especially in patients with a low transfusion burden (*clinicaltrials.gov identifier: 01736683*).[10] A parent compound is ACE 536 (luspatercept), which consists of a modified extracellular domain of hActRIIB fused to the Fc domain of hIgG1. *In vivo* studies with a mouse analog, RAP-536, showed a rapid and robust dose-dependent increase in hematocrit, hemoglobin, red blood cell and reticulocyte counts, and was hence able to both reduce and prevent anemia in the NUP98-HOXD13 MDS mouse model for over seven months.[11] SMAD2/3 activation was reduced and erythroid hyperplasia and ineffective erythropoiesis were strikingly corrected. A phase I study of ACE 536 in healthy postmenopausal women demonstrated a sustained increase in hemoglobin levels, beginning seven days after the initiation of treatment, and which could be maintained for several weeks.[12] Clinical phase II studies evaluating the erythroid response are ongoing in anemic low or intermediate-1 MDS patients who are treatment naive for hypomethylating agents (*clinicaltrials.gov identifier: 01749514*). Patients receive the drug SC every three weeks for up to five cycles. Preliminary data already suggest clinical activity, with the majority of patients demonstrating increased hemoglobin levels and/or decreased transfusion requirement accompanied by a favorable safety profile. Higher response rates were observed in patients with ring sideroblasts and/or SF3B1 mutations.[13] As a result, a placebo-controlled registration trial (Medalist) in patients with either RARS or RCMD-RS has recently been started (*clinicaltrials.gov identifier: 02631070*).

The results of the study mentioned above show that the heterogeneity and diversity of MDS is about to increase further. Strong clinical networks are required in the future to allow a fast and efficient recruitment of selected subgroups of patients into clinical trials. It has been an ambition of the ELN and the EHA SWG since 2012 to start a European initiative on clinical trials (EMSCO) in order to foster academic-driven clinical research in the field of MDS. Several clinical trials have been launched or promoted by this platform (SINTRA, EUROPE, DACOTA), and more are about to come. The experience so far has demonstrated the great heterogeneity in regulations among different countries in the EU. It is hoped that the new EU regulations (EU 536/2014), which are anticipated to be in place in 2018, will lead to a harmonization within Europe.

Mode of action of hypomethylating agents

Azacitidine, and to a lesser extent decitabine, have become the standard therapeutic approach for older patients with higher-risk disease. Responses are observed in roughly 40 to 50% of patients, including "classical" complete remission as seen in AML with conventional chemotherapy. The mode of action of HMAs has not been completely understood, but is thought to involve both a classical cytoreductive ("chemo-like") effect and also a so called "epigenetic" modulation of hematopoiesis. Recently, a study showed that clinical responses can be achieved independently of changes in the molecular burden of patients with CMML.[14] By combining serial whole-exome and whole-genome sequencing, Merlevede *et al.* showed that the response to a HMA is associated with changes in gene expression and DNA methylation, without any decrease in the mutation allele burden nor prevention of the occurrence of new genetic alterations. This is an important observation highlighting the epigenetic effects of HMAs, which might differ depending on the disease type as well as molecular background. Therefore, HMAs seem to be able to restore a disturbed hematopoiesis without affecting the size of the mutated clone. This observation mirrors clinical experience where therapy with HMAs is maintained even in the absence of classical CR or PR, but in patients achieving a hematological improvement only.

Therapeutic options for hypomethylating agents failure in patients

Although HMAs are active in many higher-risk MDS patients, the majority do not respond or lose response after an initial response. The subsequent outcome is poor with a median survival of less than 6 months, no drug having demonstrated a survival advantage at this stage, while allogeneic HSCT remains the only potentially curative option for a small subset of medically fit patients. Other patients should be offered clinical trials testing new drugs. The first randomized phase III study in that area compared standard of care (mostly supportive care only) with rigosertib, a cell-cycle inhibitor, which induces mitotic arrest *in vitro* in leukemic cells by inhibiting several kinases, including PLKs. Small phase II studies suggested that the drug has cytoreductive activity in the bone marrow of MDS patients with advanced disease. Unfortunately, the primary endpoint of this phase III trial, i.e. demonstrating a survival advantage with rigosertib, was not met (with a median survival of 8.2 *versus* 5.9 months, respectively).[15] A subgroup analysis identified that patients for whom HMAs fail within the first 9 months of therapy and those with unfavorable karyotypes seemed to benefit most from this drug. Therefore, a new trial with rigosertib in this subgroup of higher-risk MDS patients has recently been launched (*clinicaltrials.gov identifier: 02562443*).

Response criteria in MDS

The heterogeneity of MDS has challenged the evaluation of response to a given treatment. In 2006, an International Working Group (IWG) proposed a revision of standardized response criteria (IWG 2000) to evaluate clinical responses in MDS. The IWG 2006 criteria have been used in many clinical trials and served as a valuable tool for the standardization of clinically meaningful response measures in MDS. Recent clinical experiences, however, have shown that there are still some pitfalls when adopting these criteria in clinical practice, which can lead to the misinterpretation of outcome, especially with regards to erythroid response. Therefore, the ELN and EHA MDS groups, together with EMSCO, have

started an initiative to revise these criteria. We believe that the modifications (IWG 2016) will be crucial and will allow for more individualized pre- and on-study assessment and, therefore, provide the MDS community with an improved tool in terms of response evaluation.

Summary

MDS is a moving target with maximum innovation in the understanding of the complex molecular pathways during the last decade. Compared to other "chronic" hematological malignancies like myeloma or CLL this has, unfortunately, not yet been translated into novel treatment options. Given the actual developments in the field, we are optimistic that recent frustrations will be overcome and that new treatment opportunities will soon be available for our patients.

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Innovative approach to older patients with malignant hemopathies

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Introduction

Aging represents a significant health problem since nobody can escape this natural process.

Though not a disease *per se*, aging progressively leads to organ dysfunctions and represents a major risk factor for most cancers and diseases. Indeed, with the aging of the population, a 50% increase in new cancer cases is expected over the next 20 years.

Since adult stem cells are responsible for maintaining tissue homeostasis, an attractive theory is that age-related degenerative changes may be due to alterations in tissue stem cells, particularly in the hematopoietic stem cells (HSCs). Extensive research is currently underway; it demonstrates a progressive waning in our immune defenses and concomitantly, genetic and epigenetic modifications of the hematopoietic stem cells and their microenvironment.

In addition, older patients of a similar age are an extremely heterogeneous population in terms of fitness. Thus, chronological age does not adequately guide clinicians in choosing their treatment.

A better understanding of the cellular and molecular changes involved in the aging process, combined with a better assessment of the "fitness" status of older patients, will definitely help optimize and personalize therapeutic approaches in this older population in order to achieve the primary objective: healthy aging and not only prolonged survival.

Assessment of Immunosenescence

Cellular "senescence" refers to the specific phenomenon wherein a proportion of competent cells undergoes permanent growth arrest in response to various cellular stresses, translating in a replicative limit in culture, while being metabolically very active.

The definition of "immunosenescence" is still a controversial issue, but is commonly accepted as the decrease in immune function associated with aging; it combines immune deficiencies (changes in innate immune functions, shrinking of naïve T- and B-cell compartments, reduced T- and B-cell receptor diversity, decreased T-cell receptor sensi-