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FlASHback—personal highlights regarding myelodysplastic syndrome from the 2022 ASH meeting

Verena Petzer [ID] · Dominik Wolf

Summary This article intends to summarize and comment on some of the highlights regarding myelodysplastic syndrome (MDS) presented at the 2022 American Society of Hematology (ASH) annual meeting. Many abstracts dealt with the validation of the two new classifications and the International Prognostic Scoring System–Molecular (IPSS-M) being among the most intensively discussed topics in the community. Moreover, for the first time, real-world data on luspatercept were presented. Long-term data from the MEDALIST trial showed which patients benefit most from therapy with luspatercept, adding important information for the use of this substance. However, except for the phase III trial Sintra-REV, practice-changing clinical reports were sparse, although earlier trials in both higher-and lower-risk MDS reported on promising agents currently in clinical development that will hopefully improve the future management of MDS patients.

Keywords WHO classification · ICC classification · IPSS-M · Luspatercept · Lenalidomide

Introduction

During the 2022 hybrid ASH annual meeting, several interesting studies in the field were reported. To us, three main fields seem to be the most relevant and will be detailed in this article: (1) the topic of 'prognostication and classification', (2) management of lower-risk patients including real-world data on luspater-

V. Petzer (✉) · D. Wolf
Department of Internal Medicine V/Hematology and
Oncology, Comprehensive Cancer Center Innsbruck (CCCI),
Medical University Innsbruck (MUI), 6020 Innsbruck,
Austria
Verena.petzer@i-med.ac.at

cept (Bristol Myers Squibb), long-term follow-up data of the MEDALIST trial, and the final analysis of the phase III Sintra-REV study, and (3) new approaches for higher-risk patients. When appropriate, reference is made how to integrate the results into clinical practice.

Results

Classification and prognostication

At ASH 2021, the long-awaited Molecular International Prognostic Scoring System (IPSS-M) was presented and full publication immediately followed [1]. In 2022 this was the topic of numerous abstracts dealing with the validation and prognostic ability of this score in real-world cohorts among others from Europe [2] and the US [3]. It can be concluded that the IPSS-M improves the prognostic accuracy for progression-free survival (PFS) and overall survival (OS) when compared to the IPSS-R (R: revised), allowing optimized therapeutic decision making. According to one study, the IPSS-M also improved posttransplant outcome prediction (survival and prediction of relapse [2]). The latter observation highlights that the IPSS-M is potentially a better tool for hematopoietic stem cell transplantation (HSCT) candidate selection. In a broader context, this observation targets the following question: what to do with patients who are classified as lower-risk myelodysplastic syndrome (LR-MDS) according to the IPSS-R but higher-risk MDS (HR-MDS) according to the IPSS-M. In the original publication, the majority of reclassified patients were up-staged, but management of up-staged patients remains unclear [1]. Although evidence and survival data from prospective trials are currently lacking, one may consider more intensive therapy regimens for up-staged patients, including potentially

curative treatment strategies with induction therapy and consolidating HSCT. Limitations of the IPSS-M from a global view include lack of resources and highly complex analyses.

Furthermore, as two new classifications for MDS (WHO 5th edition [4] and ICC classification [5]) were introduced in 2022, validations were presented and the pros and cons of each classification were critically discussed [6]. Among many overlaps, the blast cut-off is one main difference between the two classifications and gives rise to discussion. To overcome this controversial point, Haferlach et al. presented data to exclude blast counting and categorize MDS solely based on genetic abnormalities [7]. Nine biologically distinct disease groups with substantial differences in OS could be defined by solely considering the karyotype and molecular data. The known favorable outcome of *SF3B1* mutations and isolated *del(5q)*-mutated patients together with the poor outcome of bi-allelic *TP53*-mutated patients could be confirmed. In addition, complex karyotype and *RUNX1* mutation were associated with poor outcome. Within patients carrying spliceosome mutations, *RUNX1* and *ASXL1* define distinct subgroups, harboring higher progression tendency. Overall, this discussion highlights that a detailed genetic work-up is becoming more and more important, although morphologic analysis can currently not be eliminated from any diagnostic work-up of suspected MDS and MDS/AML. However, the question of the optimal blast limit still remains a point of intense discussion.

Lower-risk MDS

In the lower-risk setting (LR-MDS), the focus was clearly set on detailed data on luspartacept (Lus) in the setting for transfusion-dependent LR-MDS with ring sideroblasts (RS) and/or *SF3B1* mutations. Final data of the phase III Sintra-REV trial and emerging therapies such as Imetelstat (Geron) were also reported.

Luspatercept

First, MEDALIST long-term follow-up data were provided and highlighted that long-term responders had the following profile: patients were younger, had a lower transfusion burden, lower serum ferritin and serum erythropoietin levels at baseline, were more likely to have mutated *SF3B1*, and less likely to have received previous ESA in the 6 months prior to study entry [8]. Even though the trial was not powered for OS/PFS analysis, luspatercept responders displayed a superior OS, whereas no difference in PFS was detected compared to the nonresponders [9].

In addition, for the first time real-world data for luspatercept confirmed MEDALIST data with respect to overall response rate of approximately 40%. Of interest, presented data also showed that transfusion independence can be achieved in patients with previous HMA or lenalidomide (Len) failure, although at lower response rates (30% HMA failure patients vs. 50% for HMA naïve patients and 33% for Len failure patients vs. 43% Len naïve patients) [10]. This study was performed in a cohort from the US, where HMA is a common treatment after ESA failure, which is usually not applied as off-label therapy in Europe.

Another real-world data set consisting of 76 patients receiving luspatercept confirmed the high response rate and beneficial safety profile [11]. According to this work, the most common reason for luspatercept discontinuation was progression to HR-MDS, but none of the patients discontinued treatment due to adverse events. However, the majority of patients discontinued their therapy at the starting dose (1 mg/kg). One should be aware that dose titration can further improve response rates, and dose escalation (up to 1.73 mg/kg) is effective, especially in highly transfusion-dependent patients. Thus, dose escalation should be performed in clinical practice before treatment discontinuation.

What all these studies on luspatercept have in common is that transfusion burden is a major predictive factor for response. The interim analysis from the phase III COMMANDS trial was recently presented at the EHA conference. Luspatercept was shown to be superior to ESA in ESA-naïve, transfusion-dependent LR-MDS patients in the first-line setting, especially among MDS patients with ring sideroblats ± *SF3B1* mutations. This highlights that early use of luspatercept is even more effective and will probably redesign the first-line treatment strategy [12].

del5(q) patients

The final results of the Sintra-REV, a phase III multicenter trial in low-risk MDS-*del(5q)* patients with transfusion-independent anemia—evaluating the use of lenalidomide vs. placebo —were presented [13]. Thereby low-dose lenalidomide (5 mg), if started before transfusion dependence, significantly prolonged time to transfusion dependency (69.8% risk reduction compared with placebo). Also response rates, both erythroid and cytogenetic, were better in the lenalidomide-treated cohort (77.8% and 94.1%, respectively). However, early use of lenalidomide did not translate into improved OS. A separate poster abstract highlighted that lenalidomide treatment is safe with regard to molecular evolution, including *TP53* mutation [14]. Based on evidence from other work [15] which raised concerns that lenalidomide can put selection pressure on *TP53*-mutated clones, the latter observation needs further attention, as patient numbers are small and the observation periods may not be long enough for the detection of a potentially harmful effect in patients with pre-existing *TP53*-mutated subclones. One major limitation to this study is that quality-of-life assessment was not reported. This would be of high interest as anemia and time to transfusion could be improved but OS was not affected. Full publication

of this work is eagerly awaited, as this may introduce lenalidomide even before transfusion independence in *del(5q)*-mutated patients.

Other LR-MDS patients

There are also promising data for patients with LR-MDS from the phase II IMerge trial investigating the telomerase inhibitor Imetelstat [16]: Platzbecker et al. presented the characteristics of patients who were non-*del(5q)*, refractory to ESA and lenalidomide, HMA naïve, and had continued transfusion independence for more than one year while on Imetelstat. Transfusion independency for >1 year was achieved in 29% of patients (median duration 92.4 weeks), thus, highlighting the high potency of this drug. In the phase III trial (NCT02598661), which was also presented at this year's EHA meeting, the primary endpoint was met (8 week transfusion independence), making this another promising treatment option for LR-MDS patients [17].

Higher-risk MDS

Only few relevant data were presented for patients with high-risk HR-MDS. Unfortunately, also after the ASH 2022 meeting the question about how to move the landscape forward for this particularly difficult-to-treat patient population remains unanswered. While there are sometimes discussions about triplet therapies, one must admit that we still do not have an approved duplet (e.g., Venetoclax/Azacitidine) therapy for HR-MDS. Results for a potential combination therapy were presented: the data of the STIMULUS-MDS1, which is a phase II trial investigating the combination of HMA (decitabine/azacitidine) plus a TIM-3 antibody (Sabatolimab®, Novartis) vs. HMA plus placebo [18], were highly disappointing. After promising results from the phase Ib study [19], the current phase II study could not meet its primary endpoint (PFS, complete remission rates). There was also no difference in OS. Only a slight benefit of the combination therapy was reported for the overall response rate (49.2 vs. 37.1%) with durable length especially among the patients achieving complete remission. The phase III STIMULUS-MDS2 (NCT04266301) study with the primary endpoint of OS has completed recruitment and will provide further information on the effect of Sabatolimab plus HMA in high-risk MDS.

Based on the phase III ASCERTAIN trial, the oral drug cedazuridine/decitabine (Taiho Oncology) was approved in the USA in 2020 for the treatment of intermediate-1, intermediate-2, and high-risk MDS [20]. In contrast, in Europe approval for MDS is still pending. At this ASH, a post hoc analysis of the phase III ASCERTAIN trial data, looking at *TP53*-mutated patients, was presented [21, 22]. Overall, 44 patients (35%) were *TP53* mutated, thereof 68% had a monoallelic mutation and 32% had a biallelic/multihit status. Although *TP53* mutation was associated with poor prognosis when compared to *TP53wt* patients (median OS 13 vs. 29.9 months), treatment with cedazuridine/decitabine revealed comparable OS data when compared to survival data for HMA treatment (9.5 months [23]). Future trials investigating this drug will be needed; thus, this drug may also serve as a backbone for combination trials in the future.

Conclusion and outlook

In addition to state-of-the-art morphological analyses, careful molecular work-up (including conventional cytogenetics/fluorescence in situ hybridization [FISH] and next generation sequencing [NGS]) should be part of every myelodysplastic syndrome (MDS) work-up. Although a better understanding of classification and prognostication is relevant for treatment decisions and the patient's overall management, treatment of MDS (in particular of higher-risk MDS) remains a huge challenge. In lower-risk disease, luspatercept will be a future standard of care as first-line therapy. Moreover, earlier treatment of *del(5q)* MDS even before transfusion dependence may be effective, even though it does not affect overall survival.

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