Highlights on Myelodysplastic Syndromes (MDS)

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SUMMARY

This ASH 2016 report will focus on the diagnostic and prognostic utility of molecular abnormalities and on new treatment modalities in MDS. We selected 7 abstracts dealing with these topics.

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CLINICAL UTILITY OF MOLECULAR ABNORMALITIES IN MDS

GENETIC ALTERATIONS PREDICT OUTCOMES IN PATIENTS WITH MDS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT)

Coleman Lindsley et al. performed targeted sequencing of 127 genes on pre-HCT blood samples from 1,514 patients who received an allogeneic HCT for MDS between 2005 and 2014. All MDS patients enrolled in the Centre for International Blood and Marrow Transplant Research (CIBMTR) Registry were considered for inclusion. Patients were excluded only if blasts were ≥20% or if they had diagnosis of Chronic myelomonocytic leukemia (CMML) or MDS/MPN (myeloproliferative neoplasm) overlap. The authors found that *TP53* mutations were the most important predictor of prognosis in allo-HCT for MDS (3 year overall survival [OS] only 20%), independent of other clinical and genetic variables. The adverse outcome in *TP53* mutated MDS was not influenced by conditioning intensity, donor type, or graft source. The OS was significantly inferior in therapy related MDS (t-MDS) patients with *TP53* mutations, but was shown to be similar in t-MDS patients without *TP53* mutations compared to patients with primary MDS. The authors conclude that the genetic lesions driving MDS pathogenesis have the potential to predict the outcome of patients following HCT.[1]

INCREASED NUMBER OF DRIVER MUTATIONS IS A PREDICTOR OF RESPONSE TO HYPOMETHYLATING AGENTS IN PATIENTS WITH MDS

Hypomethylating agents (HMA) such as azacitidine and decitabine remain the standard of care for the treatment of MDS. The presence of *TET2* mutations has been associated with an increased response in several studies. However, a clear identification of predictors of response is still required. The authors evaluated a total of 180 previously untreated patients with low- or high-risk MDS or CMML who received HMA therapy at the MD Anderson Cancer Centre. Next generation sequencing (NGS), analysing a panel of 28 genes, was performed prior to therapy with HMA. The most frequently detected mutations included *TET2, TP53* and *RUNX1* which were all present in >10% cases. No differences in overall response rates (ORR, IWG 2016 criteria) were observed based on the presence of any individual mutation. The presence of a *TET2* mutation was not significantly associated with an increased likelihood of response. Presence of three or more detectable mutations was associated with a lower ORR (OR: 0.29; p= 0.028). Patients who did not achieve a response had a significantly shorter OS and leukemia free survival (LFS). The authors concluded that the number of driver mutations could be a new biomarker to predict response to therapy with HMA in patients with MDS and CMML. Incorporating

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sequencing data at diagnosis may help to predict the response to therapy and patient outcomes.[2]

CLONAL HAEMATOPOIESIS IS ASSOCIATED WITH THERAPY-RELATED MYELOID NEOPLASMS (T-MN) IN THE ELDERLY

Clonal haematopoiesis of indeterminate potential (CHIP) is an age-dependent genetic event occurring in up to 10% of individuals over the age of 70. The authors of the abstract hypothesized that chemotherapy treated cancer patients with CHIP are at a higher risk of t-MN development. To address this, they conducted a nested case-control study to compare the prevalence of CHIP in cancer patients who later developed t-MN, to those who did not. The authors identified all patients who consented to the institutional biobanking protocol with a primary cancer preceding t-MN and an age ≥70 years at the time of either cancer. They performed targeted and whole exome sequencing of t-MN cases and described clonal evolution in cases for which paired CHIP and t-MN samples were available.[3]

Patients with t-MN had a significantly higher prevalence of CHIP prior to t-MN diagnosis when compared to matched controls (61.5% *vs.* 26.8%, p=0.02). The most commonly mutated gene in CHIP patients with t-MN was *TP53* (36.4% *vs.* 5.4% in non-T-MN patients, p= 0.02), while CHIP patients who did not develop T-MN more commonly harboured mutations in *TET2* (35%). In the majority of cases, CHIP expanded at the time of t-MN. The authors concluded that CHIP often precedes development of t-MN in chemotherapy-treated cancer patients. The distribution of CHIP-related gene mutations differs between individuals with t-MN as compared to those without t-MN, suggesting that there may be mutation-specific differences in the t-MN risk. Most CHIP mutations represented the founding leukemic mutation expanding at the time of developing t-MN. As such, these studies support the use of CHIP to inform on individualized t-MN risk.[3]

PREDICTIVE VALUE OF MUTATION ANALYSIS IN THE DIAGNOSTIC APPROACH TO PATIENTS WITH UNEXPLAINED CYTOPENIA

The diagnostic approach to unexplained cytopenia is hampered by the poor specificity of dysplastic changes that may complicate the distinction between myeloid neoplasms (MN) and non-malignant cytopenias. In the last years, several somatic mutations were identified in MN. However, the diagnostic value of mutation analysis remains unclear. In the presented study, the authors performed a mutation screening in a prospective cohort of patients with unexplained cytopenia undergoing a comprehensive diagnostic work-up, with the aim to estimate the predictive value of somatic mutations.[4]

The cohort consisted of 683 consecutive patients investigated for unexplained cytopenia at the University of Pavia, Italy, between 2003 and 2015. The diagnosis was MN in 409 cases (233 MDS, 86 MDS/MPN, 35 MPN; 55 AML) and 'other cytopenia' in 120 cases. In 154 patients a provisional diagnosis of Idiopathic Cytopenia of Undetermined Significance (ICUS) was adopted. After a median follow-up of 22 months (range 3-136), 38 patients in this category developed MN (ICUS-MN). Among patients with a diagnosis of ICUS, 57 out of 154 (37%) carried one or more mutations (Clonal Cytopenia of Undetermined Significance, CCUS). Patients with CCUS showed a significantly higher probability of developing MDS compared to those without evidence of clonality (HR: 7.48, 10-year cumulative probabilities of progression: 96% *vs.* 15% respectively, p< 0.001). The definition of a category of CCUS allows the highly sensitive recognition of patients who do not fulfil diagnostic criteria, but are at high risk of developing MDS. These data suggest that mutation analysis on peripheral blood cells may significantly improve the current diagnostic approach to patients with unexplained cytopenia.[4]

NEW TREATMENT MODALITIES IN LOW- AND HIGH-RISK MDS

INITIAL RESULTS OF A PHASE 2 STUDY OF GUADECITABINE (SGI-110), A NOVEL SUBCUTANEOUS (SC) HYPOMETHYLATING AGENT, FOR PATIENTS WITH PREVIOUSLY UNTREATED INTERMEDIATE-2 OR HIGH-RISK MDS OR CMML

Guadecitabine (SGI-110) is a next generation HMA, formulated as a dinucleotide of decitabine and deoxyguanosine, with an increased length of exposure compared to decitabine due to reduced metabolism by cytidine deaminase. A single arm, non-randomized phase II clinical trial of guadecitabine was set up for patients with newly diagnosed MDS or CMML, classified to be Intermediate-2 or High-risk by IPSS.[5] The treatment in this trial consisted of guadecitabine at a dose of 60mg/m^2 SC daily for 5 days every 28 days. The primary endpoint was complete response (CR), while secondary objectives included ORR and OS.

A total of 50 patients (43 MDS, 7 CMML) were enrolled. Half of MDS patients had a complex karyotype, one third

had t-MDS or *TP35* mutation. The ORR in this high risk population was 71%, with 32% CR, 32 % marrow CR and 7% haematological improvement. The median time to response was 3 (1-6) cycles with a median duration of the response of 4 (0-14) cycles. The median OS was 14 months. Guadecitabine was well tolerated, with a mortality rate at 8 weeks of 6%. Dose reductions were required in 34% of the patients because of cytopenias.[5]

Phase III studies will be necessary to see if guadecitabine is superior to first generation HMA. A phase III study comparing guadecitabine and treatment of choice in MDS failing HMA has already started.

COMBINED TREATMENT WITH LENALIDOMIDE (LEN) AND EPOETIN ALFA IS SUPERIOR TO LENALIDOMIDE ALONE IN PATIENTS WITH ERYTHROPOIETIN (EPO)-REFRACTORY, LOWER RISK NON-DELETION 5Q MDS: RESULTS OF THE E2905 INTERGROUP STUDY

Treatment with rhu-Epo ameliorates anaemia in a subset of low risk-MDS patients. However, the options for an effective salvage therapy are limited. In a pilot study of Epo-refractory MDS patients, addition of Epoetin Alfa (Epo Alfa) yielded erythroid responses in 28% of patients who were unresponsive to lenalidomide (LEN) alone, suggesting that LEN may overcome resistance and augment response to rhEpo. To test this hypothesis, the authors performed a randomized phase III trial comparing treatment with LEN to LEN+ Epo alfa in low/intermediate 1 risk non-del(5q) MDS patients who were refractory to, or who had a low response profile to rhEpo.[6] Patients with hemoglobin <9.5 g/dL who were unresponsive to rhEpo treatment or were transfusion dependent (>2 units/month) with serum Epo >500m U/mL were eligible for study.

In total, 195 patients were randomized to treatment with LEN 10 mg/d x21d q4wk (Arm A) or LEN + Epo Alfa 60,000U SC/wk (Arm B). The primary endpoint was IWG 2006 major erythroid response (MER) rate after 4 cycles. Among 116 patients evaluable at week 16, 33.3% and 14.3% achieved MER, respectively (p= 0.018), with a median response duration of 25.4 months *vs.* not reached. The authors concluded that LEN restores sensitivity to rhEpo in Epo-refractory low risk non-del(5q) MDS patients to yield durable and significantly higher rates of erythroid response to combination treatment without added toxicity. The results of this study support the use of combined LEN-Epo tretament in MDS low – intermediate 1 risk patients who are resistant to Erythropoiesis Stimulating Agents.[6]

LUSPATERCEPT INCREASES HAEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW-INTERMEDIATE RISK MDS: LONG-TERM RESULTS FROM THE PHASE II PACE-MDS STUDY

Luspatercept, a fusion protein containing modified activin receptor type IIB, is being developed for treatment of anaemia in lower-risk MDS. Luspatercept binds TGF-β superfamily ligands to promote late-stage erythroïd differentiation and increase haemoglobin levels. The authors report the long term results of an on-going phase II, multicentre, open-label, long-term extension study to evaluate the effects of luspatercept in patients with low-intermediate 1 risk MDS. Inclusion criteria included age ≥18 years, Hgb <10 g/dL or transfusion need ≥4U RBC/8 weeks, ESA refractory/intolerant or Epo level >500 U/L, no prior HMA, and no current lenalidomide or ESA. Luspatercept was administered subcutaneously every 3 weeks at a dose of 1-1.75 mg/kg.[7]

Data were presented for 32 extension study patients. 91% of patients were RS+ (≥15% ring sideroblasts in bone marrow). IWG HI-E (erythroid haematological improvement) was achieved in 85% of low transfusion burden patients and in 79% of high transfusion burden patients. The median time to response was 6 weeks. Of the patients with at least 2 units transfused in 8 weeks prior to dosing with luspatercept, 50% achieved RBC transfusion independence for at least 8 weeks. The duration range of transfusion independence was 9 to more than 80 weeks, with most responders still receiving treatment. Erythroïd response rates were lower in patients with high Epo levels. Luspatercept was well tolerated. The most common related adverse events were fatigue, bone pain, diarrhoea, myalgia, headache, hypertension, and injection site erythema. These data support the initiation of a Phase III study of luspatercept in regularly transfused RS+ patients with lower-risk MDS according to IPSS-R (MEDALIST study).[7]

CONCLUSIONS

Progress in the treatment of MDS is slow. About 8 years after the introduction of azacitidine for the treatment of higher-risk MDS, there is still no satisfactory treatment for MDS patients who fail on azacitidine. Second generation hypomethylating agents (HMA) such as guadecitabine are promising, but their superiority over existing HMA remains to be demonstrated in phase III studies. Erythropoiesis stimulating agents (ESA) and lenalidomide are still to be registered for the treatment of anaemia of (non del 5q) lower-risk MDS despite positive rando-

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Genomic alterations have diagnostic utility in MDS. They can detect clonal haematopoiesis in unexplained cytopenia at high risk of developing MDS. However, distinction from age related clonal haematopoiesis remains an issue.**

2 **Clonal haematopoiesis is a risk factor for the development of therapy related myeloid neoplasms.**

3 **Genomic abnormalities in MDS have prognostic and predictive utility.**
- **They may predict the response to hypomethylating agents.**
- **They may be used to refine existing prognostic systems based on clinical variables.**
- **They may predict outcome after allogeneic stem cell transplantation.**

4 **Guadecitabine is a next generation hypomethylating agent (HMA) with improved pharmacokinetic profile over decitabine and better stability after reconstitution in comparison to azacitidine. It has good activity in the frontline therapy of high risk MDS and AML. However, its superiority over existing HMA and its value in MDS failing first line HMA remains to be demonstrated.**

5 **Lenalidomide can overcome erythropoietin resistance in the treatment of anaemia of lower risk MDS. Combination therapy of lenalidomide and erythropoietin improves erythroïd response rates in comparison to single agent lenalidomide in lower risk MDS without deletion 5q after failure of erythropoietin.**

6 **Luspatercept is a TGF-b ligand trapping molecule targeting the later stages of erythropoiesis. It has a remarkable and durable effect in the anaemia of lower risk MDS with ring sideroblasts.**

mized studies. The combination of lenalidomide with ESA may overcome resistance to ESA in lower-risk MDS and is associated with better erythroïd response rates than lenalidomide alone. Luspatercept, acting at the late stages of erythropoiesis, is a promising new drug for the treatment of transfusion dependent MDS with ring sideroblasts and is now tested in a phase III study. Insights in the molecular pathogenesis of MDS are rapidly growing. At this time genomic alterations can support earlier diagnosis and refined prognostication of MDS, but targeted therapies based on molecular findings are still behind the horizon.

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