Is it already time for combination treatment in lower risk MDS?

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The term myelodysplastic syndrome (MDS) summarizes a range of different hematological disorders, which display peripheral cytopenias as common clinical characteristic. This "ineffective hematopoiesis" is thought to be a result of an imbalance of apoptotic and proliferative signals in bone marrow cells (1). Lower-risk MDS, historically defined as International Prognostic Scoring System (IPSS) low- and intermediate-1 risk (Low/Int-1) are characterized by a lower risk of turning into AML and therefore display no necessity to be treated immediately in many cases. The major risk factor for mortality and reduced quality of life in these patients represent cytopenia-related complications (e.g., infections and bleeding events). Further, red blood cell (RBC) transfusion dependence is associated with reduced survival (2). In these patients quality of life (QoL) is negatively impacted, despite intermittent physiological hemoglobin levels achieved by RBC support. Therefore, the major goal is to prevent or effectively treat chronic anemia, which is the most frequent cytopenia in lower-risk MDS.

Supportive care with RBC transfusion and administration of hematopoietic growth factors has represented the standard treatment of cytopenia in lower-risk MDS for many years. For example, treatment with erythropoietic stimulating agents (ESA) may induce erythroid responses in about 40-50% of selected lower-risk MDS patients, and the addition of G-CSF may increase this response rate (3,4). Therefore, ESA ± addition of G-CSF is considered a first line treatment for many lower-risk MDS patients with anemia.

In a distinct subgroup of patients with lower-risk MDS and a del(5q) aberration the genetic defect may constitute a target for biological therapy. In fact, lenalidomide (LEN), one of the new immunomodulating oral drugs (IMIDS) is a thalidomide structural analogue, and has been shown in several clinical trials to induce major erythroid responses in about two thirds of patients with lower-risk MDS and del(5q) including cytogenetic responses to treatment (5).

Further, a large phase II study, MDS-002 for patients with non-del(5q) low-risk MDS, has demonstrated activity including induction of transfusion independence in almost one third of patients with a median duration of response of 43 weeks (6), which is considerable lower than in the del(5q) MDS group. There is also an ongoing phase III trial in transfusion dependent non-del(5q) MDS with the aim to establish the drug as standard of care in this indication. Nevertheless, since responses are lower than in del(5q) and often short-lived combination trials aiming at improving response rates in these patients are warranted.

In lower-risk MDS, there is increased apoptosis among bone marrow hematopoietic cells, which is partially due to upregulation of TNF-α and death receptors, including FAS and TRAIL-R, and also due to decreased expression of anti-apoptotic molecules. Ezatiostat hydrochloride (Telintra) is an oral glutathione-analog reversible inhibitor of the enzyme glutathione S-transferase P1-1 (GSTP1-1), which mediates maturation of multilineage hematopoietic progenitors on the one hand, and apoptosis in cancer cells on the other hand. More precisely, recent reports have shown that ezatiostat inhibits the malignant clone by activation of the caspase-dependent apoptotic pathway and increases the reactive oxygen species in dysplastic cells, leading to apoptosis in these cells (7). These mechanistic features provide an attractive profile for modulating the biology in MDS. A previous phase II study has shown promising results in the treatment of RBC transfusion-dependent patients with an erythroid hematologic improvement rate (HI-E) of 29% (8). Further, multilineage

responses could be observed in about 30% of patients. Interestingly, the authors documented a higher hematologic improvement rate in the subset of patients who received ezatiostat after pretreatment with LEN, independently of the del(5q) aberration status. Main side effects included grade 1 and 2 gastrointestinal side effects with nausea (62%), diarrhea (33%), and vomiting (42%) (8). Finally, in contrast to LEN, which is known to induce neutropenia and thrombocytopenia in a significant proportion of patients, ezatiostat does not seem to have a myelosuppressive effect and might therefore weaken the hematologic side effects of LEN. Given these positive results Raza *et al*. conducted a phase 1 study combining these 2 drugs in 19 patients with IPSS low and intermediate-1 risk, non-del(5q) MDS patients (median age 75 years) which was published recently (7). In this trial ezatiostat treatment was applied in 2 doses (2,000 mg/day and 2,500 mg/day p.o.) in combination with LEN 10 mg p.o. on 21 of 28 days. A total of 13 patients were treated at the 2,000 mg/10 mg dose level and 6 patients at the 2,500 mg/10 mg dose level. All patients were RBC dependent or had multilineage cytopenia and received multiple pretreatment in the past including hematopoietic growth factors, chemotherapy (n=2) or LEN (n=3). Impressively, the combination was very well tolerated and no severe side effects occurred. The most frequent non-hematologic side effects were grade 1/2 anorexia, nausea/vomiting and diarrhea in half of the patients. Additionally, hematologic adverse-events occurred with thrombocytopenia grades 3/4 in 37%, neutropenia grades 3/4 in 22% and anemia grades 3/4 in 21%, respectively. These hematologic side effects might be more closely related to LEN, because they have been documented less frequently in previous single agent therapy studies with ezatiostat. After a median of four cycles 4 of 10 evaluable patients (40%) in the 2,000 mg/10 mg dose group had an erythroid hematologic improvement (HI-E) response, whereas one of 4 evaluable patients (25%) in the 2,500 mg/10 mg dose group experienced an HI-E response (7). 60% of thrombocytopenic patients had a platelet (HI-P) response. This is remarkable since single agent LEN is not able to induce platelet responses, in fact, it is rather inducing thrombocytopenia. Bilineage responses were also observed in 60% and one trilineage response occurred. All multilineage responses were documented at the 2,000 mg/10 mg dose level. The authors conclude that ezatiostat at 2,000 mg daily, combined with 10 mg LEN on days 1-21 every 28 days is safe and represents the optimal dosing for the combination of these two agents (7).

Ezatiostat, a therapeutic agent with a novel mode of action, has found its way into the treatment strategies of MDS patients. Although single agent therapy has shown significant clinical activity, the response rates might be increased by using the drug in the context of combination strategies, which play an important role in the future treatment of MDS patients.

The current study of Raza *et al*. has provided a forecast on future evolving opportunities concerning the combination of ezatiostat with other disease modifying agents in MDS. Which patient population will have the most benefit from this treatment approach and how ezatiostat might influence the disease course has to be further investigated. Currently, an ongoing phase 2 study is addressing this issue in LEN-refractory or -resistant del(5q) lower risk MDS patients (NCT01422486).

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