Facing the challenge: Novel treatment options for patients with myelodysplastic syndromes

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Introduction

Current therapeutic management for patients with myelodysplastic syndromes (MDS) is stage-dependent, ranging from growth factors and iron chelation to hypomethylating agents (HMA) and allogeneic stem cell transplantation (SCT). After years of stagnation, novel therapies are now beginning to evolve. This short review will focus on recent developments in the field.

Novel drugs to treat cytopenia in lower risk MDS

In lower risk MDS, therapy aims to improve cytopenia(s) preventing complications like bleeding or severe infections and to decrease transfusion burden.

Luspatercept and Sotatercept

Both agents are specific activin receptor fusion proteins acting as a ligand trap to neutralize negative regulators of late-stage erythropoiesis. Luspatercept (ACE-536) has recently shown promising activity to increase hemoglobin with limited toxicity in a phase 2 (PACE-MDS) study in lower-risk MDS patients. In fact, 63% of patients achieved erythroid responses with 38% achieving transfusion independence. Apart from transfusion burden and EPO levels, the presence of ring sideroblasts (RS) or SF3B1 mutation appeared to define a subgroup with a better response. These findings resulted in a placebo-controlled randomized study of luspatercept in patients with RS or SF3B1 mutation appeared to define a subgroup with a better response. This short review will focus on recent developments in the field.

Roxadustat

Roxadustat (FG-4592) is an orally administered hypoxia-inducible factor prolyl hydroxylase inhibitor currently in clinical development for anemia in MDS and CKD. Roxadustat promotes erythropoiesis through increasing endogenous erythropoietin levels and improves iron regulation by modulation of hepcidin levels. Phase 1 or 2 data in MDS are not published yet, but administration of roxadustat in mice and rats has shown to improve hemoglobin levels. Currently, roxadustat is entering a phase 3 randomized double-blind placebo-controlled study, investigating the efficacy and safety of roxadustat for treatment of anemia in patients with lower-risk MDS and low RBC transfusion burden (NCT03263091).

Imetelstat

Telomeres are thought to be critical in maintaining normal hematopoiesis. It has been shown; that MDS patients exhibited significantly shorter telomeres compared to healthy controls and higher telomerase activity (TA) was linked to a significantly inferior survival. Imetelstat is a telomerase inhibitor targeting cells with short telomere lengths and active telomerase. Single center clinical data have shown activity of imetelstat in MDS with RS phenotype. Currently, there is an ongoing phase 2/3 study in RBC transfusion-dependent and ESA-relapsed or refractory lower-risk MDS patients. Preliminary results demonstrated that 38% of patients achieved RBC transfusion-independence. Activity of imetelstat was higher in patients without del(5q) and without prior exposure to either lenalidomide or HMA.

Take Home Messages

- After several years of stagnation, novel treatment options are now evolving and tested within clinical trials covering all MDS subtypes.
- Luspatercept seems a promising novel erythropoiesis-maturating agent in lower-risk MDS.
- New liposomal daunorubicin/cytarabine formulation may re-introduce intensive treatment for a subset of higher-risk patients.
**Thrombopoietin receptor agonists (TPO-RA)**

Thrombocytopenia is present in about half of patients with lower-risk MDS. Beyond disease-modifying therapies, platelet transfusion is currently the only treatment option. Results of a randomized trial in lower-risk MDS patients treated with eltrombopag, a small molecule TPO-RA, showed 47% platelet responses versus 3% in placebo treated patients. Romiplostim has been also studied in a double blind randomized, placebo-controlled clinical trial. Thirty-six percent of patients experienced platelet response and some patients demonstrated three-lineage responses. AML transformation rate was similar for romiplostim, eltrombopag and placebo in both trials. Further studies are currently ongoing (NCT02335268).

**Hypomethylating agents (HMA)**

Standard HMA given either SC or IV have some activity also in lower-risk MDS. The oral formulation of 5-azacytidine (CC-486) may provide a more convenient way of administration and constitutes an opportunity to deliver the drug at lower doses over a prolonged period of time. A phase 3 placebo-controlled study including low- and intermediate-1 risk MDS patients with RBC transfusion-dependent anemia and thrombocytopenia (AZA-MDS-003) is currently ongoing (NCT01566695). The drug is at the moment also under investigation as maintenance therapy following intensive chemotherapy or SCT in MDS or AML patients (NCT01737535, NCT01835587).

**Novel drugs to treat higher risk MDS and secondary AML**

The principal aim of treatment in higher risk MDS is to modify the natural course of disease limiting disease progression and improving survival rates.

**First line combinations with HMAs**

Current efforts in clinical research are aiming at improving response rates with single agent HMA in higher-risk MDS. The combinations of azacytidine with either lenalidomide or vorinostat were recently investigated in a randomized trial and did not
show any benefit compared to azacytidine alone. Several studies combining HMAS with HDAC-inhibitors like pracinostat are running or have produced some conflicting results. A low-intensity approach evaluating the combination of venetoclax with azacytidine in patients with higher-risk MDS after HMA failure is currently recruiting (NCT02966782). It is known, that HMA dampen immune response by up-regulating inhibitory immune-checkpoint molecule expression while enhancing anti-tumor immune response, resulting in HMA resistance. Thus, multiple clinical trials are ongoing evaluating the combination of HMAS with immune-checkpoint inhibitors like nivolumab, durvalumab or atezolizumab (NCT02397720, NCT02775903, NCT02508870).

Studies in patients failing HMA therapy

Another important target population of clinical research are patients failing HMA treatment. Rigosertib, an inhibitor of Ras-effector pathways, is currently in a phase 3 study in this indication (NCT02562443), which demonstrated some benefit in a subset of patients. Other approaches include the use of targeted therapies with IDH-inhibitors.

CPX-351 (Vyxeos) is a novel liposomal formulation with a fixed 5:1 molar ratio of cytarabine and daunorubicin. Prior studies demonstrated accumulation of CPX-351 in the bone marrow and a selective uptake by the leukemic cell population, leading to prolonged maintenance of the target ratio with apparent improvements in efficacy. Within an open-label phase 3 study, older patients with high risk AML (incl. secondary to higher-risk MDS and failure to prior HMA) were randomized to receive induction therapy with CPX-351 or “7+3”. Median overall survival was 9.56 months with CPX-351 vs 5.95 months with “7+3”, which is a significant 31% improvement favouring CPX-351. EFS and 60-day mortality was also better in the CPX-351 arm which led to FDA approval in this indication. Thus CPX-351 is a potentially interesting option for fit higher-risk MDS patients progressing into AML, who are eligible for intensive treatment including subsequent allogeneic SCT.

Future perspectives

Given the paucity of available therapeutic options, multiple novel therapies are currently in development for MDS patients. (Figure 1). Together with the improved understanding of the pathophysiology of MDS, this set of information will hopefully evolve into personalized treatment options for patients with MDS in the future.

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