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Clinical use of ESAs in Low-Risk Myelodysplastic Syndromes

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematological diseases characterized by ineffective maturation of blood cells progenitors. The incidence of MDS is difficult to assess because of the change of diagnostic criteria over the years and the lack of an systematic registration of patients. A recent publication based on the SEER database suggests that the incidence of MDS is as high as 75 per 100,000 persons aged ≥65 years. Available data consistently suggest that MDS are predominantly a disease of the elderly and have a higher incidence among white male people; approximately 86% of patients with MDS were aged ≥60 years at diagnosis (median age, 76 years), and only 6% of cases were diagnosed in patients ≤50 years[1]. The impairment of hematopoietic bone marrow function determines variable grades of peripheral cytopenias and a propensity to evolve into acute myeloid leukemia (AML). Prognosis is poor for patients with MDS, with 3-year survival rates estimated at less than 50%. Anemia is observed in approximately 70% of MDS patients at diagnosis, leading to a relevant transfusion dependence in >80% of patients during clinical course. In low-risk MDS, anemia is the major clinical problem and may give rise to significant morbidity. This condition, more than other cytopenias, is associated with an increase risk of transfusion–related complications, alloimmunization, iron overload, cardiac failure and a significant impairment of quality of life (QoL). For these reasons one of the major goal of MDS treatment is the improvement of anemia with the aim of avoiding or delaying chronic transfusional support. Erythropoiesis stimulating factors (ESAs), alone or in combination with other grow factors, are indicated to treat anemia in low risk MDS and widely used in this setting with encouraging results. In this paper we will briefly review the main results of ESAs therapy in treating anemia in low risk MDS patients and their impact on the natural course of the disease.

Pathogenesis of Anemia in Mds

Pathogenesis of MDS is a multistep process occurring at level of totipotent hemopoietic stem cells (HSC). Several factors may contribute to ineffective hematopoiesis in MDS: 1) an abnormal activation of proapoptotic signals in progenitor cells; 2) a disregulation of signal transduction causing an excess of proinflammatory cytokines and an altered immune responses in T cells;[2-6] 3) a limited responsiveness to erythroid-stimulating growth factors[7,8]. Different studies have been conducted on erythroid progenitors (Erythroid colony forming units-CFU-E and Erythroid

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Journal of Rare Diseases Research & Treatment

burst-forming units-BFU-E) to explain the pathogenesis of anemia. It is well known that erythroid progenitors of MDS patients show an altered formation of CFU-E and BFU-E in response to endogenous EPO[9], and a profound alteration of other functional parameters such as EPO-dependent DNA synthesis and induction of GATA-1 binding activity[10]. Moreover a correlation was observed between a STAT5defective activation after EPO stimulation (with conserved STAT5 phosphorylation upon stimulation with IL3) and a block in the EPO signal transduction pathway at an early stage of erythroid development[9]. Furthermore, dyserythropoiesis has been directly linked to greater expression of proapoptotic molecules as the transmembrane mediator of apoptotic cell death Fas/CD95 in the glycophorin A subpopulation[11]. In the last decades the application of sophisticated genetic and molecular tools at diagnosis and at progression have allowed to better understanding the pathogenesis of anemia. Cytogenetic and molecular analyses have demonstrated that both normal and malignant precursor erythroid cells are stimulated by cytokine therapy. More recently the role of *Ten-Eleven-Translocation 2* and 3 (*TET2* and *TET3*) genes in human erythropoiesis has been demonstrated, opening a new scenario in understanding this phenomenon in MDS. *TET2* encodes a member of TET family enzymes that alters the epigenetic status of DNA by oxidizing 5-methylcytosine to 5-hydroxymethylcytosine (5hmC). *TET3* encodes a dioxygenase that catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in reprogramming epigenetic chromatin[12]. Knockdown experiments have demonstrated that suppression of *TET3* in CD34+ cells markedly impaired terminal erythroid differentiation as reflected by increased apoptosis without effect on erytrhoid progenitors. *TET2* knockdown led to hyperproliferation and impaired differentiation of erythroid progenitors[12].

Clinical Use of ESAs

Given the normal presence of EPO receptors on progenitor cells in MDS patients, erythropoiesis stimulating agents (ESAs) may represent an useful tool to overcome the maturation arrest and restore a normal red blood cells production. ESAs treatment has been demonstrated in clinical trials to substantially reduce or eliminate transfusion need in roughly 60% of the patients. Studies with erythropoietin and darbepoetin alfa in low-risk MDS identified transfusion independence as significant for QOL and showed primarily erythroid responses defined as International Working Group criteria: major erythroid hematological improvement in 29%-47% (HI-E) and minor HI-E in 26%-30% without improvements in platelets or granulocytes[13-19]. Recombinant Human Erythropoietin (R-Hu-EPO) alpha and darbepoetinalpha are the more frequently used ESAs for the treatment of anemia in MDS[20].

Table 1. Most significant ESAs studies in low risk MDS.

Study	N°pts	ORR
Rossi Ferrini, P.R (1998)	87	36%
Terpos, E.(2002)	281	45·1%
Park, S. (2008)	403	50%
Golshayan AR (2007)	1587	39·5%
Jädersten, M (2008)	121	39%

Table 1 summarizes the most important ESAs studies in MDS. There is general agreement that ESAs have a 40%–50% response rate, in terms of erythroid hematological improvement as defined by IWG response criteria, in low risk MDS with a median duration of response of approximately 2 years[21]. There is no difference between different ESAs formulations. Current guidelines developed by the National Comprehensive Cancer Network[22], European LeukemiaNet (ELN)[23], and European Society for Medical Oncology (ESMO)[23] are generally consistent with the management of patients with lower-risk non-del(5q) MDS. Pre-emptive treatment of asymptomatic patients is not recommended and treatment should be reserved for those with symptomatic anemia. In addition there is a limited role for addition of G-CSF based on data from a randomized phase 3 study that evaluated the role of G-CSF and found no difference between EPO versus EPO plus G-CSF[25]. However, many issues still need to be clarified, such as which patients are the ideal candidates to treatment and which is the best schedule available.

Predictive Models of ESAs Response

It has become increasingly evident that treatment with r-Hu-EPO should become "patient oriented" and different types, schedules, and duration of treatment have to be designed according to the specific criteria which most likely predict, for each individual patient, the best chance of response. The first predictive model, developed by Hellström-Lindberg and al.[13], included 94 patients across three ESA studies to determine predictors of response to a combination of ESAs and G-CSF. The model was able to discriminate 3 classes of patients with a probability of response to ESAs of 94%, 17%, and 11%, respectively. Patients with low transfusion needs (< 2 units packed red blood cell transfusions [pRBC] monthly) and a low baseline serum erythropoietin level (less than 500 IU) had a 74% chance of responding to ESAs, while those with high transfusion needs (≥ 2 units pRBC per month) and a high serum erythropoietin level (> 500 IU) had only a 7% chance of responding. Further studies have tried to refine this predictive model. Other predictors of response were reported: low IPSS score, baseline haemoglobin, no excess of blasts in bone marrow, iron status at baseline, WHO classification, karyotype, hypoplastic bone marrow, subtypes RA (refractory anemia) and RARS (RA with ring sideroblasts) and ESA-naïve at baseline[26,29]. A model based on IPSS-R score, serum EPO, and serum ferritin level may

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Journal of Rare Diseases Research & Treatment

provide additional value in predicting the response to ESAs[27.] In multivariate analysis, IPSS-R score, serum EPO, and serum ferritin level were significantly associated with erythroid response (from 85% response in IPSS-R Very Low-risk patients to 31% in Very High-risk patients). To date transfusion need, the percentage of bone marrow blasts and EPO serum level seems to be the major variables able to predict response to ESAs in low risk MDS patients[30]. For these reasons, other studies are ongoing to improve the existing predictive models of ESAs response.

Recently a new predictive score named ITACA, that better identifies ESAs non-responders, has been developed ITACA score has been validated in a cohort of 996 real-life Italian and Canadian 'good risk' MDS patients derived from a large international dataset, considers transfusion independence, erythropoietin level <100 IU/L and IPSS low-risk as independently predictive factors of response[31].

Moreover, flow cytometry analysis have been evaluated the aberrant phenotype on bone marrow precursors as strongly associated with no responders to ESAs[32-33].

Safety of ESAs Treatment

ESAs therapy in low risk MDS patients is generally safe. The most frequent adverse events associated with ESAs therapy are vascular events as thrombosis and hypertension but these events have been almost exclusively observed in solid cancer[34]. The American Society of Clinical Oncology and Hematology recommend caution when using ESAs with chemotherapeutic agents in diseases associated with increased risk of thromboembolic complications. Randomized clinical trials and systematic reviews demonstrate an increased risk of thromboembolism in cancer patients receiving epoetin or darbepoetin but specific risk factors for thromboembolism have not been defined. In the MDS setting recombinant human erythropoietin as a single drug did not increase the rate of thromboembolic events in MDS and no episodes of hypertension, seizures or cardiovascular events were reported[17,35-39]. Recently Buccisano et al have reported in a retrospective cohort of 543 MDS low risk patients treated with standard or high dose of r-Hu-EPO and darbopoietin, a low incidence (3.5%) of adverse events in particular hypertension and thrombosis, all occurred in patient treated with high dosage[40].

Conclusions

Anemia is the most vicious and disabling symptom in MDS. ESAs offer the best therapeutic alternative to transfusion support and have been proven effective in reducing chronic anemia and its clinical sequelae (e.g. fatigue, iron overload and cardiac complications). The best erythroid response rate and improvements of QoL are obtained in patients with low blast counts, low transfusion need and level of hemoglobin above 8 gr/dL. According to these results an accurate prognostic classification of MDS patient at diagnosis is a fundamental prerequisite of a correct decision making process. Even if an improvement of OS in low risk MDS patients treated with ESAs is reported, suggesting a potential role as a disease modifying agent, definitive data are still lacking. No substantial differences of efficacy or safety between r-Hu-Epo alpha and darbopoietin have been reported, but no studies of direct comparison have been conducted. The optimal dosage varies from 40.000 IU to 80.000 IU per week of r-Hu-Epo alpha corresponding to 150 to 300 of darbopoietin. Treatment should be administered at least for 12 weeks before response evaluation. ESAs are generally well tolerated and, even if they could expand red blood mass, an increased thromboembolic risk has not been demonstrated. In conclusion, in the last decade ESAs therapeutic approach have dramatically changed the natural history of low risk MDS patients. However, prospective randomized trials are warranted to clarify critical issues such as clinical or biological features predictive of response, the best timing and schedule to administer the treatment and the impact on survival.

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