Journal of Leukemia
ISSN: 2329-6917

Fuchs et al., J Leuk 2013, 1:1
DOI: 10.4172/2329-6917.1000104

Review Article Open Access

Lenalidomide Therapy of Myelodysplastic Syndromes

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Abstract

Partial or complete deletion of the long arm of chromosome 5 [del(5q)], with or without additional karyotypic abnormalities, is present in 10-15% of myelodysplastic syndromes (MDS). Anemia in these MDS responds less often to erythroblastic stimulating agents. However, immunomodulatory, anti-cytokine, and anti-angiogenic agent Lenalidomide (CC5013, Revlimid®) leads to red blood cells transfusion independence of low risk MDS with del(5q). The low risk del(5q) MDS is now recognized as a distinct pathologic subtype of MDS with markedly better clinical responses with lenalidomide treatment compared to non del(5q) MDS patients. Several mechanisms of action are believed to contribute to the therapeutic effect of lenalidomide. They include the effect on the immune system, with cytokine production, T- and natural killer cells co-stimulation, stimulation of erythropoiesis, substantional improvement in the hematopoiesis-supporting potential of bone marrow stroma and significant decrease in the adhesion of bone marrow CD34+ cells, and anti-inflammatory effects and angiogenesis inhibition. The exact mechanism of action of lenalidomide on del(5q) clones is not known, but there appears to be several candidate (tumor suppressor) genes whose expression may be modulated by lenalidomide treatment. The addition of lenalidomide inhibited the *in vitro* proliferation of erythroblasts harboring del(5q) while the proliferation of cells from normal controls and cells without 5q deletion was not affected. Patients with mutated *TP53* were shown to have poorer erythroid and cytogenetic responses to lenalidomide and a higher potential for acute myeloid leukemia (AML) evolution. The mechanism of lenalidomide action is different in non-del(5q) MDS, where lenalidomide restores and promotes effective erythropoiesis without direct cytotoxic effect. Recent trials have focused on combining lenalidomide with other agents active in MDS.

Keywords: del(5q) MDS; MDS without 5q Deletion; Lenalidomide; Erythropoiesis; Cell cycle; Apoptosis; Adhesion; SPARC; Phosphatases; p53

Abbreviations: AML: Acute Myeloid Leukemia; AP1: Activator Protein 1; CD: Cluster of Differentiation; DIAPH1: Diaphanous-Related Formin; FISH: Fluorescence In Situ Hybridization; EPO: Erythropoietin; HRQL-Health-Related Quality of Life; ICAM1: Intracellular Adhesion Molecule 1; IFN: Interferon; IL: Interleukin; IPSS: International Prognostic Scoring System; IRAK1: Interleukin-1 Receptor-Associated Kinase; MDS: Myelodysplastic Syndrome; NF-κb: Nuclear Factor κb; RBC: Red Blood Cell; RPS14: Protein of Small Ribosomal Subunit 14; SDF-1: Stromal Cell-Derived Factor 1; SNP: Single Nucleotide Polymorphism; SPARC: Secreted Protein Acidic and Rich in Cysteine; STAT: Signal Transducer and Activator of Transcription; TIRAP: Toll-Interleukin-1 Receptor Domain-Containing Adaptor Protein; TNF: Tumor Necrosis Factor; TRAF6: Tumor Necrosis Factor Receptor-Associated Factor-6; VEGF: Vascular Endothelial Growth Factor

Introduction

Interstitial deletions involving long (q) arm of chromosome 5 are one of the common cytogenetic abnormalities in MDS patients [1-14]. The presence of del(5q), either as the sole karyotype abnormality or as part of a more complex karyotype, is present in 10-15% of patients with *de novo* MDS and has distinct clinical implications for MDS [1]. Outcomes among MDS patients with deletion 5q vary greatly, both in terms of overall survival (OS) and risk of transformation to AML. The presence of additional chromosomal abnormalities or an excess of blasts shortens OS and increases risk of transformation to AML. Del(5q) MDS patients frequently have symptomatic anemia, and its treatment has traditionally consisted of red blood cell (RBC) transfusions and, for some, iron chelation therapy. The 5q- syndrome, a subtype of low risk MDS, is characterized by an isolated 5q deletion. Although the length of the deleted area varies from case to case, deletion in the band 5q32-33 is common. The 5q- syndrome is characterized by a female predominance, severe refractory macrocytic anemia, normal or elevated platelet counts, abnormal hypolobulated megakaryocytes, stable clinical course with relatively rare progression to acute myeloid leukemia (AML). MDS with isolated del(5q) in which the sole cytogenetic abnormality is del(5q) is a distinct entity with the risk of evolution into AML of approximately 10% [11,15]. It is characterized by macrocytic anemia with or without other cytopenias and/or thrombocytosis. Myeloblasts comprise less than 5% of bone marrow and less than 1% of peripheral blood.

Lenalidomide [3-(4-amino-1-oxo1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione; Revlimid; Celgene Corporation, Summit, NJ, USA] is 4-amino-glutarimide analog of thalidomide with potent immunomodulatory, antiangiogenic and direct neoplastic cell inhibitory activity [16-23]. Thalidomide was synthesized in Germany, in 1954, from α-phtaloylisoglutamine, to be used as a sedative and antimetic drug. In 1957, after a short period of preclinical studies, thalidomide was approved for first trimester gestational sickness in humans. The appearance of malformations, such as phocomelia in the newborn, resulted in its ban three years later [21-23]. The US Food and Drug Administration (FDA) approved thalidomide in 1998 for the

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Received February 10, 2013; **Accepted** March 27, 2013; **Published** March 29, 2013

Citation: Fuchs O, Jonasova A, Neuwirtova R (2013) Lenalidomide Therapy of Myelodysplastic Syndromes. J Leuk 1: 104. doi:10.4172/2329-6917.1000104

treatment of erythema nodosum leprosum [24]. A small but consistent fraction of transfusion-dependent MDS patients achieved transfusion independence by treatment with thalidomide [25-27].

Lenalidomide was developed in order to avoid thalidomide side effects (sedation and neuropathy), and to increase efficacy [16-21]. Lenalidomide shares a number of structural and biological properties with thalidomide but it is safer and more potent than thalidomide. Lenalidomide was first studied in a single- center trial [28]. Erythroid and cytogenetic responses were achieved in a study of 43 patients with MDS, particularly in patients with isolated del(5q31-33) [28]. Lenalidomide was administered in three different dosing schedules: 25 mg daily, 10 mg daily, and 10 mg daily for 21 days of each 28-day cycle [28]. The erythroid response rates were highest in patients with the International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS. Transfusion independence was achieved in 20 of 32 patients (63%), and three additional patients had reduced red blood cells transfusion needs [28]. Ten of 12 patients (83%) with del(5q31) experienced major erythroid responses, defined as sustained transfusion independence, compared with a 57% response rate in patients with a normal karyotype and a 12% response rate in patients with other cytogenetic abnormalities. Complete cytogenetic remissions were achieved in 75% of the del(5q31) patients (9 of 12 of these patients), with one additional patient achieving at least a 50% decreases in abnormal metaphases [28]. Myelosuppression (neutropenia and/or thrombocytopenia) was the most common adverse event, but it was dose-dependent, favoring the 10 mg daily dose for 21 days of each 28-day cycle.

Multicenter Phase II Trials of Lenalidomide

After encouraging results of a single-center trial (MDS-001) [28] (Table 1), the effect of lenalidomide on red blood cell (RBC) transfusion-dependent del(5q) MDS cases of low and intermediate-1 IPSS risk assessment was investigated in a large multicenter phase II study (MDS-003). This trial led to FDA approval of lenalidomide in the USA as well as to approval in several other countries for treatment of RBC transfusion-dependent anemia due to low or intermediate-1 risk MDS associated with a chromosome 5q deletion with or without additional cytogenetic abnormalities [29]. The initial schedule was 10 mg of lenalidomide for 21 days every 4 weeks, but the treatment schedule was subsequently amended so that the 10 mg dose was given every day because of the shorter interval between initiation of treatment and a response in the pilot study. Of the 148 transfusion-dependent patients who were included in the study, 46 were treated on the 21-day schedule and 102 received continuous daily dosing. Overall, 112 (76%) patients responded to treatment with a median time to response 4.6 weeks. Among these, 99 no longer needed transfusions by week 24, while the remaining 13 patients had a reduction of 50% or greater in the number of transfusions required. There was no significant difference in response rate between the two treatment schedules. Response rate was independent of additional chromosomal aberrations. Patients with pretreatment thrombocytopenia had an inferior outcome. Almost half of the patients, including some with complex karyotypes, had a complete cytogenetic response. Neutropenia and thrombocytopenia were the most common treatment-associated adverse events. Most other adverse events were of low or moderate severity and included pruritus, rash, diarrhea, and fatigue. Adjustment of the lenalidomide dose due to intolerance was required in 124 patients, including 93 of those receiving continuous daily dosing and 31 of those receiving 21-day dosing. Thirty patients discontinued lenalidomide treatment because of adverse events including thrombocytopenia or neutropenia, rash AML, anemia, facial edema, congestive heart failure, urticaria, diarrhea, weight loss, renal insufficiency, cerebrovascular accident, dementia, dyspnea, pyrexia, and pneumonia.

However, the European Medicine Agency (EMA) did not approve lenalidomide for this indication. Their concern, based on results of the MDS-003 trial, was that lenalidomide may trigger progression to AML in some patients with del(5q). Data comparing long-term outcomes in lenalidomide-treated and untreated patients with MDS with del(5q) are limited but it is now clear that the concern of the EMA has not been confirmed by a recent study [30].

Kuendgen et al. [30] have evaluated clinical outcomes of 295 lenalidomide-eated patients from two clinical trials (MDS-003 and MDS-004, Table 1) and 125 untreated red blood cell transfusion-dependent patients with del(5q) low- or intermediate-1-risk MDS from a large multicenter registry. Median follow-up was 4.3 years from first dose for lenalidomide-treated patients and 4.6 years from diagnosis for untreated patients. Risk factors for AML progression and mortality were assessed. In conclusion, lenalidomide treatment did not increase AML progression risk, but instead confered a survival benefit in red blood cell transfusion-dependent patients with del(5q) low- or intermediate-1-risk MDS.

The long term effect of lenalidomide on the 5q-syndrome was investigated retrospectively in 168 patients treated in four MDS trials [31]. For those patients who achieved transfusion-independency, the median duration of response was 2.2 years. In multivariate analysis cytogenetic response, lower bone marrow blast percentage, and lower baseline transfusion burden were independent predictors of prolonged overall survival.

Current recommendation state that treatment with lenalidomide in del(5q) MDS should be continued until disease progression [32]. The question whether interrruption of lenalidomide treatment for patients in remission would be beneficial has been also addressed [33]. It is important for several reasons: 1) it could reduce costs and side effects; 2) it could facilitate disease progression to AML. Different mechanisms have been discussed to explain AML progression. Evidence that pre-therapeutic telomere length was significantly shorter in those patients who ultimately transformed to AML than in those who did not, was presented [34]. Transformation to AML is occasionally observed, paticularly in patients without a cytogenetic response to lenalidomide. Jädersten et al. [35] performed molecular studies in a patient with classical 5q- syndrome with complete erythroid and partial cytogenetic response to lenalidomide, who evolved to high-risk MDS with complex karyotype. Immunohistochemistry of pretreatment marrow biopsies revealed a small fraction of progenitors with overexpression of p53 and sequencing confirmed a *TP53* mutation. *TP53* mutated subclones have not previously been detected in 5q- syndrome and indicates heterogeneity of this disease. Subsequently, *TP53* mutations with a median clone size of 11% (range, 1% to 54%) were detected in 10 from 55 (18%) low-risk MDS or intermediate-1 risk patients with del(5q) by next-generation sequencing [36]. *TP53* mutations are associated with strong nuclear p53 protein expression. Patients with mutation had significantly worse outcome. *TP53* mutations may lead to genetic instability and disease progression. This clonal heterogeneity in low-risk MDS patients with del(5q) may be of importance when assessing the prognosis and selecting the therapy in these patients. It has been speculated that continuous administration of lenalidomide may lead to selective pressure on stem cells that induces genomic instability, resulting in acute leukemia transformation [37].

Trial	Lenalidomide dose	Number of patients	Results	Comments
MDS-001 phase I/II study	Varying doses of oral lenalidomide, ranging from 25 mg daily down to 10 mg for 21 days of every 28-day cycles [28].	43 patients with MDS and transfusion-dependency or symptomatic anemia. All patients were refractory to erythropoietin or had high endogenous erythropoietin levels. 88% of patients had low- or intermediate-1 risk IPSS risk assessment. 60% of patients had del(5q) chromosomal aberration.	This study showed the potential of lenalidomide in erythropoietin-resistant del(5q) MDS but also a role of lenalidomide in erythropoietin-refractory non-del(5q) MDS patients. 83% of patients with del(5q31) MDS responded compared to 53% of patients with a normal karyotype and 12% of patients with other karyotype abnormalities [28].	Responses were definied according to the modified International Working Group (IWG) criteria [61]. Neutropenia and thrombocytopenia were common side effects.
MDS-002 phase II study	10 mg of lenalidomide orally either for 21 of 28 days, or with continuous dosing [42].	215 patients at a median age of 71 years with low or intermediate-1 risk MDS with or without non-del(5q) chromosomal abnormalities.	26 patients were identified as transfusion-independent with a median hemoglobin rise of 3.2 g/dL. A further 17% achieved a reduction of pretreatment transfusion requirements. The duration of response was at least 24 weeks.	Ebert et al. [59] identified a set of erythroid-specific genes with decreased expression in non-del(5q) MDS responders on patient samples from this trial.
MDS-003 phase II study	10 mg of lenalidomide orally for 21 of 28 days with possible dose reductions in case of adverse events to 5 mg daily and 5 mg daily every other day [29].	148 transfusion-dependent, lower-risk, del(5q) patients. 111 had a single del(5q) chromosomal abnormality, and 37 patients had additional chromosomal abnormalities.	64% of patients became transfusion-free (at least 56 days of transfusion independence) and at least 1 g/dL increase in hemoglobin. 44% of patients achieved a complete cytogenetic remission (absence of the del(5q) cytogenetic abnormality).	MDS-003 was a single-arm study. Factors predicting response to lenalidomide in del(5q) MDS were a platelet count decrease by at least 50% in non-thrombocytopenic patients at base-line (before starting with lenalidomide treatment).
MDS-004 phase III study	10 mg of lenalidomide orally for 21 of 28 days, 5 mg of lenalidomide on days 1 to 28, or placebo on days 1 to 28 of 28-day cycles [65].	205 del(5q) MDS patients were randomized 1:1:1 to lenalidomide 10 mg/day, lenalidomide 5 mg/day, or placebo in the double-blind treatment phase.	56.1% of patients treated with 10 mg of lenalidomide, 42.6% of patients treated with 5 mg lenalidomide and 5.9% of patients with placebo achieved red blood cell transfusion independence for at least 26 weeks. Median time to response was about 4 weeks, median maximum of hemoglobin increase was 6.3 g/dL. Complete cytogenetic response rates were 29.4%, 15.6%, and 0% for lenalidomide 10 mg, lenalidomide 5 mg, or placebo.	52 patients (25.4%) progressed in this phase III study to AML with almost 3 years of follow-up.
MDS-005 phase III study	10 mg of lenalidomide orally once daily (administered as one 10 mg lenalidomide capsule and 2 placebo capsules) or placebo (3 placebo capsules) once daily for up to 4 years (see Steensma DP-The Hematologist March 1, 2011 and Celgene MDS 005).	375 low risk (low- or intermediate 1-risk) MDS patients without del(5q) who do not respond to erythropoiesis-stimulating agent therapy and require regular red blood cell transfusions.	Study start date: November 2009; estimated study completion date: December 2018; estimated primary completion date: April 2016 (final data collection date for primary outcome measure).	clinicaltrials.gov Identifier: NCT01029262 (A servise of the U.S. National Institutes of Health). This international a phase III trial, double-blind is being conducted at more than 70 medical centers in 14 countries, including 9 centers in the United States and Canada.

Table 1: Trials in lenalidomide approved for use in MDS by the United States Food and Drug Administration (FDA).

Longest transfusion-free intervals are achieved in patients low-risk MDS patients with del(5q) who are exposed to lenalidomide 6 months beyond complete cytogenetic remission [33,38-41]. Lenalidomide should not be withdrawn prematurely in patients who achieve transfusion independence as partial cytogenetic remission patients seem to have a higher relapse rate than complete cytogenetic remission patients.

Response rate to lenalidomide in low- or intermediate-1-risk MDS without a 5q deletion was investigated also in a multicenter, phase II study (MDS-002) [42] (Table 1). 214 patients received 10 mg oral lenalidomide daily or 10 mg on days 1 to 21 of a 28-day cycle. The most common grade 3/4 adverse events were neutropenia (30%) and thrombocytopenia (25%). 56 (26%) patients achieved transfusion independence after a median of 4.8 weeks of treatment with a median duration of transfusion independence of 41.0 weeks. A 50% or greater reduction in transfusion requirements occured in 37 additional patients, yielding a 43% overall rate of hematologic improvement (in comparison with 76% in the case of low- or intermediate-1-risk MDS patients with del(5q)). Responding karyotypes included trisomy 8 (n=3), -Y (n=3), deletion 11q (n=2), and deletion 17p (n=1). While clonal suppression represents the main mechanism of lenalidomide action in MDS patients with del(5q), the restoration and promotion of effective erythropoiesis is the main mechanism in non-del(5q) MDS patients [43].

Sibon et al. [44] have recently reported 31 lower-risk non-del(5q) MDS patients with anemia refractory to erythropoiesis-stimulating agents (ESA) and treated with lenalidomide. Twenty patients from this group also received an ESA. An erythroid response was obtained in 15 patients (48%), including 10 of the 27 (37%) previously transfusion-dependent patients, who became transfusion-independent. Nine of responders relapsed, whereas 6 (40%) were still responding and transfusion free after 11 months. Median response duration was 24 months.

These studies were based on scientific knowledge because small deletions in several ribosomal genes, including *RPS14*, were found in CD34+ cells not only in patients with del(5q) but also in patients with non-del(5q) MDS. This observation suggested that deregulated ribosomal biogenesis may not be limited to del(5q) MDS [45-47]. Czibere et al. [48] showed that lower risk non-del(5q) MDS patients with *RPS14* haploinsufficiency tend to have prolonged survival. Defective ribosomal biogenesis has a lead role in disrupting erythropoiesis in a variety of anemias. Disruption of ribosomal biogenesis has been clearly demonstrated in multiple ribosomopathies to greatly perturb p53 signaling [49-58].

Bone marrow aspirates of patients who responded to lenalidomide showed before treatment decreased expression of the set of the genes needed for erythroid differentiation. Lenalidomide seems to overcome differentiation block in del(5q) patients with decreased expression of these genes compared to the non-responders [58]. Thus, lenalidomide restored erythroid differentiation potential by upregulation of the

suppressed erythroid gene signature (genes for α- and β-globin, ankyrin 1, band 3, band 4.2, carbonic anhydrase, ferrochelatase and glycophorin B) [59].

The "Groupe Francophone des Myélodysplasies" conducted a multicenter phase 2 trial with lenalidomide in intermediate-2 (19 patients) and high-risk MDS (28 patients) with del(5q) [60]. Forty seven patients (24 males and 23 females, with a median age of 69 years, range, 36-84 years) were treated. Forty three patients of 47 patients had transfusion-dependent anemia. Patients received 10 mg lenalidomide once daily orally during 21 days every 4 weeks. In patients without response after 8 weeks, the lenalidomide dose was increased to 15 mg/day in the same time schedule during an additional 8 weeks. If no response was found in this additional time of treatment, lenalidomide was discontinued. Thirteen of the 47 patients (27%) achieved response according to International Working Group (IWG) 2006 criteria [61]. Median duration of overall response was 6.5 months, 11.5 months in patients who achieved the complete remission. Grade 3 and 4 neutropenia and thrombocytopenia were seen in most patients.

Möllgård et al. [62] hypothesized that increasing doses of lenalidomide may be successfully used in high-risk MDS and AML with chromosome 5 abnormalities. They tested this hypothesis in prospective phase II multicenter trial with 28 patients (12 with intermediate-risk 2 or high-risk MDS and 16 with AML). Oral lenalidomide was given at a dose of 10 mg/day in weeks 1 to 5. The dose was increased to 20 mg/day in weeks 6 to 9, and to 30 mg/day in weeks 10 to 16. In the case of suspected drug-related toxicity the dose was lowered to 5 mg/day. The overall response rate in treated patients with MDS was 36% (4/11) and that for AML patients was 20% (3/15). Seven patients stopped therapy due to progressive disease and nine because of complications, most of which were disease-related. Patients with *TP53* mutations responded less well than those without mutations. No responses were observed among 11 cases with deleterious *TP53* mutation [62].

Randomized Phase III Placebo-controlled Study of Lenalidomide in del(5q) Patients

This study [63-67] (Table 1) examined the safety of lenalidomide in a randomized phase III trial (MDS-004) in low-/int-1-risk myelodysplastic syndromes (MDS) with a del(5q) abnormality.

Similar criteria to those used in the MDS-003 study were chosen. Two hundred five patients were randomized to receive treatment with either lenalidomide 10 mg orally daily for 21 days of each 28-day cycle, lenalidomide 5 mg orally daily for 28 days of each 28-day cycle, or placebo. Erythroid responses were assessed at 16 weeks. Nonresponders were then in open-label treatment and they were excluded from the efficacy analysis. Red blood cell transfusion independence was achieved in 53.6% of patients treated on 10 mg arm, 33.3% on 5 mg arm and 6% on the placebo arm. Cytogenetic response rates were also highest in the 10 mg arm (41.5% of patients), while in 5 mg arm (17.4%) and in the placebo arm (0%). The median rise in hemoglobin at the time of the best response was also higher in patients treated with the 10 mg lenalidomide. No difference in the rate of AML transformation among three arms was found. This study confirmed that the preferred starting dose of lenalidomide in patients with del(5q) low-/int-1-risk MDS remains 10 mg.

Health-related quality of life (HRQL) outcomes were assessed using the Functional Assessment of Cancer Therapy-Anemia in 167 RBC transfusion-dependent patients with IPSS low- or intermediate-1-risk del5q31 MDS treated with lenalidomide versus placebo in a randomized phase III clinical trial, MDS-004 [67]. Clinically important changes in HRQL from baseline were observed at weeks 12, 14, 36, and 48 among responders in both treatment groups (5 mg and 10 mg lenalidomide). Lenalidomide treatment may be effective in improving HRQL outcomes [67].

Further Clinical Studies of Lower Risk MDS Patients with Del(5q) Treated with Lenalidomide

Many of the initial clinical and laboratory observations obtained in the MDS-003 trial were confirmed in the study of Le Bras et al. [68]. Ninety five lower risk MDS patients (low and intermediate 1 risk in IPSS, 25 males and 70 females with a median age of 70.4 years) with del(5q) were treated with 10 mg of lenalidomide daily, 21 days every 28 days for at least 16 weeks. Patients with at least a minor erythroid response after 16 weeks were treated in the same way until disease progression, treatment failure or treatment-limiting toxicity.

Erythroid response was evaluated according to IWG 2000 criteria [69]. Sixty two of the 95 patients (65%) achieved erythroid response according to IWG 2006 criteria [61]. In these 62 patients, 60 patients (63% from 95 patients) achieved red blood cell transfusion independence. Median time to transfusion independence was 16 weeks (range 8-33 weeks). Fifteen patients who achieved transfusion independence were analyzed for cytogenetic response (20% of complete and 40% of partial cytogenetic response). The rest of these 15 patients (40%) had no cytogenetic response. Six (6.3%) patients progressed to AML and 15 patients died, including 6 patients who had achieved transfusion independence. In the MDS-003 trial, the primary endpoint was hematological response, while in the study of Le Bras et al. transfusion independence. The cytogenetic remission rate was higher in the MDS-003 trial (73% versus 60% in the study of Le Bras et al. [68]). Neutropenia and thrombocytopenia were the most common adverse events in both studies [70].

A Japanese multiinstitutional study MDS-007 in MDS patients with del(5q) treated with lenalidomide has been recently performed [71,72]. This study was targeted on morphologic analysis and evaluation of the relationship among erythroid response, change of morphologic findings and cytogenetic response. MDS-007 trial was a single-arm, open-label study. Eleven patients were enrolled in this study, including 5 patients with transfusion-dependent anemia and 6 patients with transfusion-independent symptomatic anemia. Nine patients showed less than 25% of bone marrow erythroblasts before therapy with lenalidomide and no patient had more than 40% of bone marrow erythroblasts at that time. Eight patients showed a rapid increase of bone marrow erythroblasts to more than 40% on day 85. All patients except one achieved a major erythroid response as defined by either transfusion independence or by rapid increase of hemoglobin level in most patients on day 169 of lenalidomide therapy. One patient without any hematologic response by day 169, achieved a major erythroid response on day 218. Erythroid response could be achieved even without a cytogenetic response. No patient in this analysis showed a hematological relapse prior to cytogenetic one. These findings suggested that lenalidomide can improve anemia by more than one mechanism of action and also through mechanism different from del(5q) elimination.

Treatment of del(5q) Patients with Relapse during Lenalidomide Exposure

At the time of relapse of transfusion dependence, bone marrow aspiration would be performed in order to evaluate the patient for morphological or cytogenetic progression. If there is no progression,

the patient is without drug next 3 to 4 monthes. Thereafter, the patient is re-exposed to lenalidomide. Second responses are regularly seen, probably by epigenetic mechanism [73]. In the case of progressive disease, salvage therapies including demethylating agents or allogeneic bone marrow transplantation are necessary [74].

Therapy with Lenalidomide in Combination with another Drug in MDS

In order to maximize the potential benefit from lenalidomide therapy combination strategies were developed. Lenalidomide in attempt to improve outcome of patients can be combined with erythropoiesis-stimulating agents (ESA), such as erythropoietin or darbepoietin alpha. This therapy is based on preclinical observations showing that lenalidomide significantly potentiated erythropoietin receptor signaling. The addition of erythropoietin (40,000 U/week) for an additional 8-week course had the beneficial effect in low and intermediate-1 risk MDS patients who had failed prior treatment with lenalidomide monotherapy for 16 weeks [75]. To evaluate the potential benefit of the combination of lenalidomide and ESA, Park et al. [76] tried the association in three del5q MDS patients, who were resistant or partially responding to lenalidomide alone. Lenalidomide had two different actions, one on the disapperance of the 5q-clone and the other one on the stimulation of the erythroid production in combination with ESA.

In low to intermediate-1 risk non-del(5q) MDS, lenalidomide treatment is less effective with a lower response rate (25%) and shorter response duration than in the same risk MDS with del(5q) [41]. Combination of lenalidomide with another drug could improve outcome of patients with low to intermediate-1 risk non-del(5q) MDS. Ezatiostat hydrochloride (Telintra, TLK199), a tripeptide glutathione analog is a reversible inhibitor of the enzyme glutathione S-transferase P1-1 (GSTP1-1) inhibitor [77-83]. This inhibitor was developed for the treatment of cytopenias associated with lower risk MDS. Ezatiostat activates jun-N-terminal kinase (JNK), promoting the growth and maturation of hematopoietic progenitors, while inducing apoptosis in human leukemia blasts [77]. The ability of ezatiostat to activate the caspase-dependent pathway may help eliminate or inhibit the emergence of malignant clones. Alternatively, ezatiostat increases reactive oxygen species in dysplastic cells and contibutes by this effect also to apoptotic death [77]. Based on these mechanisms of action, response rates, non-overlapping toxicities, and tolerability observed in a single agent ezatiostat phase 1 and 2 studies in MDS [79-81,84], a study of the combination of ezatiostat and lenalidomide was conducted to determine the safety and efficacy of ezatiostat with lenalidomide in non-del(5q) low to intermediate-1 risk MDS. Eighteen patients (median age 73 years; range 57-82; 72% male) were enrolled in the study [81]. Thirteen patients (72%) were intermediate-1 risk and 5 patients (28%) were low risk. Four patients had abnormal cytogenetics. Twelve patients (67%) were red blood cell transfusion-dependent and 2 patients (11%) were platelet transfusion-dependent. Three of 8 (38%) patients achieved transfusion independence including 1 responder who did not respond to prior lenalidomide. Ezatiostat caused clinically significant reduction in red blood cell and platelet transfusions. Since ezatiostat is non-myelosuppressive, it is a good candidate for combination with lenalidomide. The recommended doses of this combination regimen for future studies is the ezatiostat.

Lenalidomide and azacitidine are active in patients with lower- and higher-risk MDS. These agents may complement each other by targeting both the bone marrow microenvironment and hypomethylating action on the malignant clone. Phase I combination trial of lenalidomide and azacitidine in patients with higher-risk MDS was a multicenter, single-arm, open-label study [85]. Twenty five patients were screened and enrolled in this therapy and their response was assessed after four and seven cycles of the tretment. Azacitidine was administered at 75 mg/m^2 daily for five consecutive days, and lenalidomide 10 mg daily for 21 days, of a 28-day cycle. Of 18 evaluable patients, 12 (67%) responded to therapy; 8 (44%) achieved complex response, 3 (17%) had hematologic improvement and one (6%) had bone marrow complex response. Of those who responded, eight experienced relapse or disease progression at a median 7.5 months from initial response (range, 3 to 17 months). Two patients transformed to AML, one patient at 7 and one patient at 11 months from initial response. Another report from the same research group on three MDS patients with normal cytogenetics who relapsed on monotherapy and achieved a complete response with combination of lenalidomide and azacitidine has been recently published [86]. This combination was also studied by the other American, French, German and Australian groups [87-90]. The combination of lenalidomide and azacitidine is feasible and seems to be effective in lower risk MDS with del(5q) [88] and even in a very high risk patient groups with advanced MDS or AML and a del(5q) [85-87,89,90].

Romiplostim (AMG 531, Nplate) is an Fc-peptide fusion protein (peptibody) that acts as a thrombopoietin receptor agonist. It has no amino acid sequence homology with endogenous thrombopoietin. Romiplostim stimulates megakaryopoiesis and thrombopoiesis by binding to and activating the thrombopoietin receptor and downstream signaling [91-94]. Romiplostim appeared well tolerated in patients with lower risk MDS and thrombocytopenia [95]. Low platelet counts in patients with MDS may be due to the underlying disease or due to treatment with disease-modifying agents, and platelet transfusions are often the only treatment for clinically significant thrombocytopenia or bleeding. Randomized phase II study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk MDS receiving lenalidomide was performed [96]. This was double-blind, placebo controlled, dose finding study that evaluated the effect of romiplostim on the incidence of clinically significant thrombocytopenia events (grade 3 or 4 thrombocytopenia and/or receipt of platelet transfusions) and the safety of romiplostim in patients with low or intermediate-1 risk MDS receiving lenalidomide. Thirty nine patients (median age 74 years; range, 39 to 90) were randomized into treatment groups receiving placebo, 500 μg romiplostim, or 750 μg romiplostim by weekly subcutaneous injections in combination with lenalidomide (one 10 mg capsule by mouth daily for each 28-day cycle). Fifteen patients (39%) had platelet counts$<50\times10^9$/L and 7 (18%) had del(5q). Treatment continued for a total of four cycles. Twelve patients (31%) discontinued the study. Disease progression to AML was reported in 1 patient in the romiplostim 500 μg group. Response was 8% for the placebo, 36% for 500 μg romiplostim, and 15% for 750 μg romiplostim groups. Romiplostim appeared to be well tollerated in low or intermediate-1 risk MDS patients receiving lenalidomide.

It is possible that the effect of lenalidomide could be augmented by addition of another immunomodulation agent, cyclosporine A. A single-arm, open-label study of the efficacy and safety of lenalidomide in combination with cyclosporine A in red blood cell transfusion-dependent both 5q- and non 5q- MDS patients started at Weill Cornell Medical College in New York.

Other drugs are tried and will be probably used in combinations with lenalidomide in the treatment MDS patients with del(5q) in the future. Dexamethasone and lenalidomide rescue erythropoiesis, alone

and in combination, in RPS14- and RPS19- (ribosomal proteins of small ribosomal subunit) deficient cells [97]. L-leucine was also studied in RPS14- and RPS19- deficient cells [98-101]. The combined use of L-leucine and lenalidomide might be considered for therapy in MDS patients with the del(5q) since there is evidence to suggest that these two drugs act through different mechanism and their effect may be synergistic.

Mechanisms of Action of Lenalidomide

Lenalidomide shares a number of structural and biological properties with thalidomide**,** but it is safer and more potent than thalidomide. Both drugs appear to function through four mechanisms: immunomodulatory, anti-inflammatory, anti-angiogenic and direct neoplastic cells inhibitory [102,103]. Lenalidomide has a direct erythropoiesis stimulating effect. Shortly, Wei et al. [104] demonstrated that the haplodeficient enzymatic targets of lenalidomide within the commonly deleted region are two dual-specificity phosphatases, the cell division cycle 25C (Cdc25C) and the protein phosphatase 2A (PP2A). These phosphatases are coregulators of G2-M checkpoint in the cell cycle and thus, their inhibition by lenalidomide leads to G2 arrest and apoptosis of del(5q) specimens. The mechanism of action is different in non-del(5q), where lenalidomide restores and promotes effective erythropoiesis with no direct cytotoxic effect [104]. Lenalidomide promotes erythropoiesis and fetal hemoglobin production in human CD34+ cells [105]. The increased fetal hemoglobin expression was associated with epigenetic effect on chromatin (an increase in histone 3 acetylation on the γ-globin gene promoter).

In MDS patients with del(5q), allelic deletion of the *RPS 14* gene is a key effector of the hypoplastic anemia. Impairment of ribosomal biogenesis liberates free ribosomal proteins to bind to and trigger degradation of HDM2 (human homologue of the mouse double minute 2 protein /MDM2/) with consequent p53 transactivation in response to nucleolar stress independently of DNA damage [106,107]. Overexpression of p53 is typical for erythroid precursors of primary bone marrow of MDS patients with with del(5q). Lenalidomide inhibits the haplodeficient PP2A resulting in hyperphosphorylation of inhibitory serine 166 and serine 186 residues on MDM2, and displaces binding of RPS14 to suppress MDM2 autoubiquitation whereas PP2A overexpression promotes drug resistance. Lenalidomide promotes p53 degradation by inhibiting HDM2 autoubiquitination in erythroid precursors of MDS patients with with del(5q) bone marrow [108].

The similar epigenetic modulation of gene for p21(CIP1/WAF1) by lenalidomide was described in both lymphoma and multiple myeloma [109]. A potent cyclin-dependent kinase inhibitor p21(CIP1/WAF1) decreases activity of cyclinE-CDK2 or cyclinD-CDK4/6 complexes, and thus functions as a regulator of cell cycle progression. The p21 protein can mediate cellular senescence and also interact with proliferating cell nuclear antigen (PCNA), a DNA polymerase accessory factor, and plays a regulatory role in S phase DNA replication and DNA damage repair.

Most MDS patients including those with del(5q) become refractory to erythropoietin (EPO). EPO is an essential glycoprotein that facilitates red blood cell maturation from erythroid progenitors and mediates erythropoiesis [110]. EPO acts through EPO-receptor (EPO-R) and the signal transducer and activator of transcription 5 (STAT5) [43,111]. Disruption of STAT5 results in a variety of cell-specific effects, one of which is the impaired erythropoiesis [108]. Lenalidomide relieves repression of ligand-dependent activation of the EPO-R/STAT5 pathway. Ebert et al. [59] showed that target genes of this pathway are underexpressed in lenalidomide-responsive MDS patients wihout del(5q). Lenalidomide promotes erythropoiesis in MDS by CD45 protein tyrosine phosphatase inhibition [112]. CD45 phosphatase is overactivated in MDS and may inhibit phosphorylation of STAT5 stimulated by EPO-R. Lenalidomide is able to restore EPO-R/STAT5 signaling that is essential for hematopoiesis. Lenalidomide restores and promotes effective erythropoiesis in non-del(5q) without direct cytotoxic effect.

A deregulated immune system plays the important role in pathogenesis of MDS. Deregulation is caused by the alteration of cytokines in the bone marrow microenvironment, deffective T-cell regulation and diminished natural killer (NK) cell activity. Deficiences in T cells, NK cells and interferon-γ (IFN-γ) production were described in the bone marrow and peripheral blood of MDS patients [113,114]. Lenalidomide exhibits potent T-cell costimulatory properties and augmented production of IL-2 and IFN-γ [16,115]. Akt (proteinase B) signaling pathway and transcription factor AP1 (activator protein 1) are involved in T-cell activation [115]. Increased numbers and activation of NK and NK T-cell populations were also observed in peripheral blood cells cultured with lenalidomide [116,117].

Anti-inflammatory effects of lenalidomide is based on inhibition of proinflammatory cytokines and chemokines, such as TNF-α, IL-1β, IL-6, IL-12, monocyte chemotactic protein-1 and macrophage inflammatory protein-1α. On the other hand, lenalidomide elevates anti-inflammatory cytokine IL-10. Interestingly, haploinsuficiency of miR-145 and miR-146a in 5q - syndrome increases IL-6 levels by elevation of interleukin-1 receptor-associated kinase 1 (IRAK1), Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP), tumor necrosis factor receptor-associated factor-6 (TRAF6), and NF-κB [118-120]. RPS14, miR-145, and miR-146 were significantly increased and TNF-α, IL-1β and IL-10 significantly downregulated during the treatment with lenalidomide [121-123].

Angiogenesis, the formation of new blood vessels, plays an important role in the growth and progression of MDS. The vascular endothelial growth factor (VEGF) and to a lesser extent IL-6 are cytokines that stimulate the formation of blood vessels. Increased levels of these cytokines have been shown in MDS [124]. Anti-angiogenic effects of lenalidomide are independent of immunomodulatory effects and are mediated through endothelial cell migration inhibition [125-128]. The mechanism by which lenalidomide inhibited VEGF-induced endothelial cell migration may be related to VEGF-induced inhibition of Akt phosphorylation. Furthermore, loss of anti-angiogenic effect of lenalidomide predicted disease progressionand an increased risk of transformation to AML [129].

Lenalidomide does not affect DNA synthesis but inhibits cytokinesis of MDS cells. Cytokinesis occurs as the final stage of cell division after mitosis. A contractile ring, made of non-muscle myosin and actin filaments assembles in the middle of the cell adjacent to the cell membrane. Formins are Rho-GTPase effector proteins that are involved in the polymerization of actin and effects microtubule during meiosis, mitosis, the maintenance of cell polarity, vesicular trafficking and signaling to the nucleus [130,131]. Diaphanous (mDia)-related formin mDia1 is encoded by *DIAPH1* located on the long arm of chromosome 5 (5q31.3) and lies between the two commonly deleted regions in MDS patients with 5q- syndrome. It is not clear whether mDia1 plays a role in lenalidomide effect on cytokinesis. Knock-out of *DIAPH1* in mice has T cell responses and myelodysplastic phenotype [132-134].

The clinical effect of lenalidomide is associated with significant increases in the numbers of erythroid, myeloid and megakaryocytic colony-forming cells and a substantial improvement in the hematopoiesis-supporting capacity of bone marrow stroma. Lenalidomide induces significant alterations in the adhesion profile of hematopoietic progenitor cells, including over-expression of membrane ligands (CXCR4/CD184, CD54/ICAM1, CD11a and CD49d where CD is cluster of differentiation) and overproduction of soluble stromal cell-derived factor-1 (SDF-1) and of ICAM1 in the bone marrow microenvironment. CXC4 is C-X-C chemokine receptor type 4 also known as fusin or CD184. ICAM1 (intracellular adhesion molecule 1 also known as CD54) is a cell surface glycoprotein. All these effects favor the maintenance of CD34+ cells in the bone marrow [135]. Lenalidomide-mediated induction of the SLAM antigen CD48 on patients' CD34+ cells may be associated with the drug's apoptosis-inducing effect through co-stimulatory interactions between CD34+ cells and cytotoxic lymphocytes in the bone marrow microenvironment.

Conclusion and Perspectives

Lenalidomide is currently the treatment of choice for lower risk transfusion-dependent del(5q) MDS patients, and remains a treatment alternative for the management of anemia in lower risk MDS without 5q deletion MDS patients with adequate neutrophil and platelet counts [136]. Lenalidomide has also activity in higher risk MDS and AML with del(5q) and even in non(del5q) MDS.

Though the mechanism of lenalidomide action has not been definitively determined, it is clear that there is a difference between mechanisms in MDS with del(5q) and MDS with non-del(5q).

In MDS with del(5q), lenalidomide acts through inhibition of phosphatase activity in the commonly deleted region of the long arm of chromosome 5. This phosphatases play a key role in cell cycle regulation. The inhibition of these phosphatases by lenalidomide leads to G2 arrest, followed by apoptosis of del(5q) specimens. The direct cytotoxic effects of lenalidomide on the del(5q) clone are also very important. Lenalidomide inhibits the malignant clone and up-regulates the *SPARC* (secreted protein acidic and rich in cysteine) gene mapping to the commonly deleted region in 5q- syndrome patients [137]. However, SPARC is dispensable for murine hematopoiesis [138]. While haploinsufficiency of the *RPS14* gene appears to be a key contributor to erythropoietic failure associated with del(5q) MDS, the critical genes responsible for clonal dominance in del(5q) high-risk MDS and AML are less well-defined. It is known that this deleted region is different in del(5q) high-risk MDS and AML [139]. The effect of lenalidomide in these cases needs to identify further biologic features accounting for the response, thereby allowing rational use of this drug, both alone and in combination with another agents.

In MDS with non-del(5q), an increased expression of adhesion molecules caused by lenalidomide treatment leads to recovery and maintenance of the CD34+ cells through interactions between the hematopoietic and stromal cells. This effect of lenalidomide on the bone marrow microenvironment causes abrogation of the function of pro-apoptotic and pro-inflammatory cytokines. Lenalidomide is capable to increase red blood cell production independently of ribosome dysfunction. Lenalidomide restores and promotes effective erythropoiesis without direct cytotoxic effect. Lenalidomide activates the EPO-R/STAT5 pathway.

New cytogenetic tools such as fluorescence in situ, hybridization (FISH) or single nucleotide polymorphism array (SNP-A)-based karyotyping, increased the diagnostic yield over metaphase cytogenetics. Sugimoto et al. [140] have recently found with help of these new cytogenetic tools that normal karyotype and gain of chromosome 8 were predictive of response to lenalidomide in non-del(5q) patients with myeloid malignancies.

The presence of multiple cellular and genetic abnormalities in MDS is common and suggests that combination therapy targeting different mechanisms of action may be beneficial, particularly in higher-risk disease, for which both microenvironment and cell regulatory mechanisms play a role. The optimal dose, schedule and duration of treatment is still an area of active investigation, especially in the use of lenalidomide combinations with other drugs.

Acknowledgments

This work was supported, by PRVOUK-27/LF 1/2. The research grant NT/13836-4/2012 from the Ministry of Health of the Czech Republic and by the project (Ministry of Health, Czech Republic) for conceptual development of research organization (Institute of Hematology and Blood Transfusion, Prague).

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