Management of Multiple Myeloma and Myelodysplastic Syndrome: Focus on Lenalidomide

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Abstract: Lenalidomide belongs to a group of immunomodulatory drugs (IMiDs), first known with the discovery of thalidomide in the 1950s, and which have then been tested in various malignancies for their clinical potential. It is described that these IMiDs exhibit multiple biologic effects on cytokine and cell-mediated responses. Lenalidomide was developed by chemical modification of thalidomide to enhance the immunomodulatory potency but minimize the dose-limiting neurotoxic effects. This drug seems to have a positive clinical impact on hematologic malignancies including myelodysplastic syndrome, multiple myeloma, and chronic lymphocytic leukemia. Different potential mechanisms are discussed for lenalidomide, including inhibition of angiogenesis, blockade of various cytokines and enhancement of immune system function. Even with strong improvement of the outcome of multiple myeloma, still most patients relapse and, therefore, drugs with new mechanisms of action are urgently needed to overcome this resistance. As for myelodysplastic syndromes, a heterogeneous collection of hematopoietic disorders characterized by cytopenia, treatment options also have increased over the past 10 years, but still supportive care, cell-stimulating agents and chemotherapy with little impact on long-term outcome are offered to patients.

In this review, we discuss the impact of lenalidomide on relapsed myeloma and transfusion dependent MDS as a novel strategy under assessment in preclinical and clinical trials. It was shown that Lenalidomide had clinical potential in both entities and its effectiveness might be enhanced by the rational combination with conventional agents.

Keywords: multiple myeloma, MDS, lenalidomide

Introduction

Multiple Myeloma (MM) is a malignant plasma cell disorder first documented with a case report in 1844. Even if many scientists and clinicians have put much effort in understanding the pathomechanism, optimizing diagnostic procedures and therapeutic strategies, MM remains to be incurable in nearly all cases until today. Based on the results of Alexanian et al melphalan was the main therapeutic agent introduced in the 1960s. Despite the improvement of progression free and overall survival through the implementation of high dose melphalan and autologous stem cell transplantation it took more than 30 years until an alternative therapeutic agent became crucially important. Thalidomide which was introduced to the market in 1957 was popular for its sedative effect and the treatment of morning sickness in pregnancy. Unfortunately it is associated with severe teratogenic malformations so that it was withdrawn in 1961. Concurrently with the withdrawal thalidomide was considered to have anti-cancer activity. Thalidomide is still used clinically as therapeutic agent for leprosy, Behcet disease and HIV and was approved by the FDA 1998 for the treatment of erythema nodosum. In a compassionate use program with 84 patients Barlogie et al could demonstrate remission rates of 32% in MM patients. For the first time in 30 years a different medication than melphalan indicated single agent activity. The results observed in a study of the University of Arkansas could be confirmed by other study groups in patients with newly diagnosed, refractory or relapsed MM. Unfortunately the treatment with thalidomide goes along with an unfavorable toxic side effect profile, mainly polyneuropathy, sedation, constipation and thromboembolic events. With the intention to reduce these side effects and to optimize the therapeutic efficacy, numerous analogs of thalidomide were synthesized. Lenalidomide known as
CC-5013 became the most promising substance and established a new class of agents, the immunomodulatory drugs, so called ImiDs.

A second entity where scientists and clinicians recently focused on lenalidomide as a new treatment option are the myelodysplastic syndromes (MDS). This group of heterogenic disorders arises from bone marrow stem cells with an abnormal cellular maturation and thus is characterized by a dysplastic, yet ineffective hematopoiesis. These irreversible cellular defects in hematopoietic cells result in peripheral chronic cytopenia, such as anemia, neutropenia, and thrombocytopenia. MDS is a disease of the elderly with a median age at diagnosis between 60 and 70 years, and among hematological disorders it is the most frequent occurring malignancy for patients older than 70 years. During the course of the disease approximately 30% of MDS cases transform into acute myelogenous leukemia (AML) which is often refractory to standard treatment.

The attempt to classify this heterogeneous disease in regard to define treatment strategies and prognostic evaluation was proven to be difficult. First based solely on cell morphology and bone marrow blast counts, MDS was separated into five subgroups and was then refined by WHO taking cytogenetics and uni—or multilineage dysplasia into account. Studies then showed that with these additional factors survival and disease progression could be predicted more reliably. The cytogenetic abnormalities also had impact on therapeutic strategy guidelines where four risk categories (IPSS) were suggested based on percent of marrow blasts, specific cytogenetic abnormalities, and number of cytopenias. Before, for about 20 years, MDS management was mostly unspecific and symptomatic treating the consequences of cytopenia like increased risk for infection and bleeding as well as symptomatic anemia with transfusions and supportive antibiotic care. With understanding underlying pathogenetic mechanisms of these molecular changes novel treatment approaches were introduced in addition to the established supportive care. There are three common chromosomal abnormalities in MDS, deletions of chromosomes 5 and 7 and trisomy of chromosome 8. The chromosomal abnormalities are more likely in patients with secondary MDS, found in about 90% of the cases, occurring as a late toxicity of previous cancer treatment (radiation and/or alkylating chemotherapy) compared to approximately 50% in primary MDS patients. The disease severity and treatment resistance increases with more complex aberrations in the karyotype requiring more intensive therapy including 5-azacytidine and decitabine as well as cyclosporine A and ATG. In this review, we focus on subgroups with either an isolated deletion of chromosome 5, referred to as 5q-syndrome, as well as on complex karyotypes including the del5q, where prognosis has strongly improved with the introduction of lenalidomide in the therapeutic strategy.

Mechanism of Action of Lenalidomide

The interaction of multiple myeloma cells with bone marrow stroma cells (BMSc), osteoblasts, osteoclasts and endothelial cells as well as the impact of the BM milieu via secretion of cytokines, anti-apoptotic factors and growth factors plays a crucial role in MM pathogenesis and drug resistance. Therefore the basic approach for development, identification and validation of novel therapeutic agents is to intervene in different proliferative and anti-apoptotic signaling cascades. Lenalidomide is one of these new therapeutic agents which target not only the MM cell, but also cell-host interactions, cytokine-secretion as well as the BM milieu. The pathomechanism of action of thalidomide and other immunomodulatory drugs is not fully understood. It is well established that thalidomide and lenalidomide have an anti-angiogenetic effect via the decrease of VEGF secretion. The anti-inflammatory component of the IMiDs is achieved through the inhibition of pro-inflammatory secretion of cytokines of activated monocytes and macrophages with lenalidomide having a 100–50000 times higher potency of inhibition compared to thalidomide. Aside from TNF-α (tumor necrosis factor) there is also the fact that distribution of ILs-1β, −12 and −6, cyclooxygenase-2 and TGF (transforming growth factor) is inhibited. The immunomodulatory impact of the IMiDs is obtained through the stimulation of the T-cell activity, which results in an enhanced secretion of interferon-γ and IL-2. Interferon-γ and IL-2 activate the clonal T-cell-proliferation and natural killer (NK) cell activity augmenting T-cell and NK cell-mediated lysis of i.e. myeloma cells. Additionally, lenalidomide seems to enhance the cellular response to recombinant erythropoietin
in erythroid progenitors in MDS, while granulocyte-monocyte-macrophage progenitors are not affected. It is discussed that lenalidomide reverses the inhibition of the EPO signaling. Furthermore, a pro-apoptotic effect could be demonstrated and this appears to be of vital importance for the action of this thalidomide-analogue. Beside this pro-apoptotic effect of lenalidomide, a recent study by Pellagatti et al postulated that response to lenalidomide in patients with del5q may depend on selective growth inhibition of erythroblasts but not of cytogenetically normal cells. Thus, lenalidomide seems to alter the gene expression profile in del5q by up regulating the SPARC gene expression, a tumor-suppressor gene, located in the 5q region, with antiproliferative and antiadhesive properties. But even if all IMiDs have similar effects on the inflammatory cytokine secretion, every IMiD present with a unique profile of T-cell modulation, degree of anti-angiogenesis intensity and expression of adhesion molecules. This may indicate the intended use of specific IMiDs for selected diseases. CC-5013 was approved by the FDA for the treatment of 5q-syndrome and for the therapy of relapsed or refractory MM, whereas in Europe, so far only an approval for relapsed of refractory MM is assigned.

**Efficacy of Lenalidomide Monotherapy or in Combination with Dexamethasone in Patients with Multiple Myeloma**

In a phase I dose escalation study with 27 patients with refractory or relapsed MM Richardson et al considered 25 mg as maximum tolerated dose. Importantly, no significant somnolence, constipation, or neuropathy has been seen in any cohort. In this cohort of pre-treated patients best response of at least 25% reduction in paraprotein occurred in 17 (71%) of 24 evaluable patients (90% CI, 52%–85%), including at least 50% reduction in paraprotein in 7 (29%) of 24. In 2005 Rajkumar et al published data of a phase II trial with lenalidomide and dexamethasone for previously untreated myeloma patients. According to the response criteria of the European Group for Blood and Bone Marrow Transplant (i.e. Blade’ criteria) 31 of the 34 patients (91%) achieved an objective response with a decrease in serum monoclonal protein level by 50% or greater and a decrease in urine M protein level by at least 90% or to a level less than 200 mg/24 hours. Forty-seven percent of patients experienced non-hematological side effects such as grade III to IV including fatigue, muscle weakness, anxiety, pneumonia and rash. In newly diagnosed patients the combination of lenalidomide and dexamethasone is highly effective with manageable side effects.

Two phase III, placebo controlled trials (MM-009 and MM-010) investigated the efficacy of lenalidomide plus dexamethasone versus dexamethasone alone in the treatment of relapsed or refractory MM. 704 patients (353 of the MM-009 study + 351 of the MM-010 study) who had received at least one previous antimyeloma therapy were randomly assigned to receive 25 mg of oral lenalidomide or placebo on days 1 to 21 of a 28-day cycle. In addition, all patients received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. Patients were excluded from the study with the occurrence of disease progression or unacceptable toxic effects. The time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone compared to the patients who received placebo (MM-010 median, 11.3 months vs 4.7 months; P < 0.001 respectively in the MM-009 median, 11.1 months vs 4.7 months; p < 0.001). A complete or partial response occurred in 60.2% (MM-010) and 61% (MM-009) of the patients in the lenalidomide group and in 24% (MM-010) and 19.9% (MM-009) of the patients in the placebo group (P < 0.001), respectively. The overall survival was significantly improved in both studies in the lenalidomide/dexamethasone groups (not reached in MM-009 and 29.6 month in MM-010 versus 20.6 and 20.2 month; p < 0.001 for both studies).

Of the 704 patients receiving lenalidomide/dexamethasone, 39% were treated with thalidomide previously. Nevertheless lenalidomide/dexamethasone treatment led to a more significant overall response rate (ORR) and progression free survival (PFS) compared to the placebo group. The toxicity profile was similar in patients with or without prior thalidomide therapy.

The conclusion of both studies is that lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory MM. The results of these studies were the rationale for the approval of lenalidomide in
combination with dexamethasone for patients with MM in first relapse of the FDA and the EMEA.

Recent results of the E4AO3 study 2008 by the Eastern Cooperative Oncology Group (ECOG) were presented by Rajkumar et al.\textsuperscript{30} In this randomized trial lenalidomide plus high-dose dexamethasone (RD) was tested versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed myeloma. While patients in the high-dose dexamethasone arm received 480 mg/cycle, patients in the low-dose dexamethasone arm received 160 mg/cycle. 445 patients were enrolled in this study. The over all response rate was significantly higher in the RD arm than in the Rd arm (82\% vs 70\%, \(p = 0.007\)). Nevertheless the over all survival was significantly superior with Rd, \(p = 0.006\). A reason might be the higher rate of early deaths and grade III and IV toxicities in the RD arm (50\% vs 30\%, \(p < 0.001\)), thus leading to an earlier discontinuation of treatment in the RD arm.\textsuperscript{30} A longer follow up is needed to substantiate these data. The findings of this study provoked a discussion about the empirically chosen dosage of high dose dexamethasone and settle the question of whether high doses of dexamethasone are necessary, especially with the availability of new drugs.

**Efficacy of Lenalidomide Monotherapy in Patients with Myelodysplastic Syndromes**

One hallmark of MDS is an ineffective erythropoiesis which is difficult to manage. Therefore novel treatment strategies are needed for patients with transfusion-dependent or symptomatic anemia. The initial safety and efficacy studies tested lenalidomide in a phase I/II trial in MDS patients with diverse karyotypes and red cell transfusion-dependent disease or symptomatic anemia.\textsuperscript{31} Prior to the study the majority of these patients had already failed treatment with erythropoietin. Twenty-four of the evaluable patients (56 percent) had either sustained transfusion independence or more than 50\% reduction in the need of transfusion upon treatment with lenalidomide after 16 weeks. The response rate was highest in patients with 5q-syndrome and in those with low/intermediate1 IPSS scores. In MDS patients with 5q-deletion a restoration of a normal karyotype was found in nine out of twelve patients. Dose dependent myelosuppression was the most common adverse event which required dose reduction or interruption of treatment in 58 percent of the patients.\textsuperscript{31} As Lenalidomide seemed to have the strongest beneficial potential on erythropoiesis in low/intermediate1-risk patients and with 5q syndrome,\textsuperscript{32} a large multicenter Phase II trial with 148 patients was initiated.\textsuperscript{33} Patients received either 10 mg of lenalidomide daily or for 21 days every four weeks. Response to the treatment was assessed after 24 weeks. Seventy-six percent of the patients achieved a reduction of transfusion and 67 percent a transfusion independence after lenalidomide treatment. In 5q-syndromes complete and partial cytogenetic responses were achieved in 45 and 28 percent of evaluable patients, respectively. About a third of these patients maintained a complete resolution of cytological dysplasia. Responders to treatment remained transfusion-free for an average of 2.2 years. In this preliminary report a 10-year survival was estimated for those patients with a cytogenetic response. The most common adverse events were grade 3 and 4 neutropenia and thrombocytopenia in 55 and 44 percent, respectively as shown in the phase I trial as well. The above results were shown in patients with low or intermediate-1 risk MDS patients. In the latter trial by List et al.\textsuperscript{33} a small number of patients had an IPSS score of intermediate-2 or high risk (but all patients had a del5q) where a transfusion-independence was achieved in about 30\% of the patients. Morphological response was not affected by the complexity of karyotype aberrations so that even in 75\% of patients with blast excess a complete cytogenetic response was obtained. But, however, in the follow-up of these MDS patients, fewer patients remained responders compared to patients with a 5q-syndrome. Lenalidomide efficacy in patients with del 5q in combination with other chromosomal abnormalities need to be assessed in larger trials including advanced MDS stages like AML with del 5q and therapy-induced MDS with del 5q as there are only limited reports. Additionally, the primary treatment goal in patients with advanced stages is different from those patients with low/intermediate disease. In the latter one transfusion independence is the primary goal where it lengthens of survival in the other group.

A phase II study by Raza et al investigated the efficacy of lenalidomide in MDS patients with karyotype abnormalities other than del 5q.\textsuperscript{34} The 214 evaluated patients with transfusion-dependent MDS but low/intermediate-1 risk required more
than 2U of RBC in the last 8 weeks prior treatment. Administration and dosage of lenalidomide was according to the previous phase II trial for del 5q patients. Twenty-six percent of the patients achieved transfusion-independence and an additional 17% had a reduction of transfusion of 50% or more. Compared to patients with del5q, patients with other karyotype abnormalities had a shorter median duration of disease improvement with about 41 weeks versus 2.2 years, respectively. Still, these low/intermediate risk patients had a clinically meaningful effect on erythropoiesis upon treatment with lenalidomide. A recent study by Ebert et al showed that the response rate of patients lacking the del5q can be predicted by using gene expression profiling. A molecular signature was detected consisting of a cohesive set of erythroid-specific genes involved in erythroid differentiation. Responders to lenalidomide showed a decreased expression of this gene subset resulting in erythroid differentiation. This is of importance for those patients who did not benefit from recombinant erythropoietin and with lack of other treatment options.

**Lenalidomide in Combination with Other Cytotoxic Agents**

To evaluate the safety and efficacy of the combination of lenalidomide and chemotherapy in patients with MM a phase I/II trial was conducted. 62 patients received liposomal doxorubicin 40 mg/m² i.v. and vincristine 2 mg i.v. on day 1, dexamethasone 40 mg p.o. on days 1–4 (DVd), and lenalidomide on days 1–21 in 28-day cycles. The MTD of lenalidomide with DVd chemotherapy was 10 mg. After 7.5 months of median follow-up, the ORR of the combination was 75%, with 29% of patients achieving a complete or near complete remission. The median progression-free survival was 12 months. The combination of lenalidomide and DVd chemotherapy was well tolerated and resulted in high response rates in this mostly refractory patient population. Clarithromycin plus lenalidomide/dexamethasone (BiRD) was given to newly diagnosed patients for a 90.3% ORR with a CR rate of 38.9%, while the ≥VGPR rate was 73.6%. Another study investigated the combination of lenalidomide with cyclophosphamide and dexamethasone. Based on in vitro data it was postulated that the addition of an alkylating agent to lenalidomide and dexamethasone could increase response rates. Twenty-one heavily pre-treated patients were given lenalidomide, cyclophosphamide and dexamethasone in a 28 day cycle for a maximum of 9 cycles. The side effect profile was as expected with a dose reduction or withdrawal of cyclophosphamide in 48% of patients and a dose reduction of lenalidomide in 24% of patients. Deep vein thrombosis occurred in 14% of patients. The ORR (CR + PR) was 65%. In summary, being aware of the small number of patients, the combination of RCD is effective in pre-treated patients and has manageable toxicities, but the authors suggest due to the frequency of neutropenia a dose reduction of cyclophosphamide.

To evaluate the safety and efficacy of the association of Melphalan/Prednisone/Revlimid (MPR) as induction treatment for newly diagnosed myeloma patients over age 65 or those under 65 years who refuse or are not eligible for high dose therapy a randomized placebo-controlled multicenter phase III study was conducted. Previous data of a phase I/II trial showed a response rate of 81%, including 48% VGPR and 24% CR, while 1-year EFS and OS rates were 92% and 100% respectively. Data of the phase III trial are expected to be published soon. New data of safety and efficacy for lenalidomide when used in combination therapy with bortezomib, dexamethasone, cyclophosphamide (VDCR) in newly diagnosed patients with multiple myeloma were presented by Kumar et al. Twenty-six patients were enrolled in a phase I dose escalation study. The overall rate of serious AEs was 40%. According to the uniform response criteria, response rates were 100% ≥ PR, 68% ≥ VGPR. Richardson et al reported similar results in 68 myeloma patients to Kumar et al with a comparable ORR of 98% ≥ PR and 71% ≥ VGPR. In this dose escalation study an ORR of 100% is achieved with the maximum dosage. The efficacy was independent of baseline cytogenetics or ISS stage. Various combination regimens are currently under investigation, especially promising three and four drug combination therapies i.e. Lenalidomide, Melphalan, Prednisone and Thalidomide (RMPT). For previously untreated patients a phase I/II study of bortezomib and lenalidomide was recently published. Response rates and prolongation of PFS could be improved significantly with the addition of novel drugs to the standard regimen of melphalan/prednisone, but it remains to be proven that these superior response rates can be transmitted into a prolonged survival.

Clinical Medicine: Therapeutics 2009:1
The future challenge is to determine the optimal combination and sequence of the available therapeutic agents.

In the matter of MDS there are ongoing trials of lenalidomide alone or in combination with other reagents in MDS patients where the results are awaited. For lenalidomide as a single agent, the most effective and safe dosage as well as the course of treatment is not yet exactly determined. It seems that the dosage tolerated in MDS patients is lower than in patients with multiple myeloma (5 to 10 versus 25 mg). The result of this MDS 004 trial where a 5 vs 10 mg daily dosage was compared is still pending. However, based on these available data, the FDA approved a restricted use of lenalidomide in patients with transfusion-dependent anemia in low or intermediate-1 risk MDS patients, mainly associated with a del 5q with or without additional cytogenetic abnormalities.

Preliminary results from a small patient cohort of seven MDS patients in a phase I trial who received in addition to lenalidomide 5’-azacitidine, described a complete response 50% of the four evaluable patients. One patient had an erythroid response. These results need further evaluation but they suggest a potential efficacy.

**Lenalidomide and the Most Common Side Effects**

Published data for lenalidomide/dexamethasone demonstrate high rates of venous thromboembolism (VTE). The risk significantly increases in analogy to the experience with thalidomide in case of combination with chemotherapy or erythropoietin. In the earlier mentioned two phase III studies of lenalidomide/dexamethasone combination therapy with no recommended anticoagulation, VTE occurred more often in the lenalidomide group compared to the placebo group with 14.7% vs 3.4% (MM-009) and 11.4% vs 4.6% (MM-010). A randomized double blind placebo controlled trial for previous untreated MM patients compared dexamethasone in combination with lenalidomide versus high dose dexamethasone alone. A high initial rate of VTE was seen in newly diagnosed myeloma patients treated with lenalidomide/dexamethasone; therefore ASA 325 mg was mandated. Of 198 patients, 25 patients developed a VTE (12.6%) during initial therapy with lenalidomide/dexamethasone or after cross over while 7 patients (3.5%) had VTE in the high dose dexamethasone arm. Reducing the incidence of VTE is critical to patient survival, as approximately one fourth of pulmonary embolism (PE) cases present as sudden death. The heterogeneity of published data does not allow a particular recommendation for VTE prophylaxis for patients receiving an immunomodulatory-based therapy. The optimal pharmacological VTE prophylaxis for patients treated with a combination regime with dexamethasone or chemotherapy and immunomodulatory drugs remains controversial.

Data of the ongoing study with aspirin, fixed dose warfarin or low molecular weight heparin in patients with MM, are expected to be published soon. As long as there are no published data which prove the equality of the different strategies, VTE prophylaxis may be administered according to the guidelines of the American Society of Clinical Oncology (ASCO). In addition the recommendation according to a risk assessment model based on various risk factors may be helpful.

A limiting toxicity of lenalidomide is myelotoxicity with many patients experience neutropenia, thrombocytopenia of anemia. Myelotoxicity is manageable with the concurrent use of growth factors and attentive dose reductions. The risk of infection is very likely increased in combination with dexamethasone. A consideration about the use of lenalidomide before stem cell harvest is, that it may limit the success of stem cell collection. Therefore no more than 6 month of therapy should be given before the approach of collection. In contrast to thalidomide, lenalidomide is not associated with significant neuropathy, constipation or fatigue.

In case of impaired renal function the therapy with lenalidomide may become challenging. Renal impairment does not alter the oral absorption, protein binding, or nonrenal elimination of lenalidomide, but the renal lenalidomide clearance decreased drastically in patients with severe renal dysfunction. Therefore dose adjustments are needed for patients with a creatinine clearance [CL(Cr)] < 50 ml/min.

Overall, side effects of lenalidomide in MDS patients are similar to those described in multiple myeloma. Myelotoxicity in MDS patients seems to be more severe (grade 3 and 4) compared to patients with multiple myeloma due to the disease characteristics such as cytopenia. This appeared to be particularly pronounced in MDS with del5q. Therefore full blood count monitoring is mandatory.
during the first two month of treatment. Current recommendations for treatment with lenalidomide include administration of G-CSF when neutrophils are below $1 \times 10^9/l$ and transfusion of platelets when required. In some cases dose reduction or treatment discontinuation is needed. Patients with MDS should be informed about VTE and it is recommended to interrupt treatment in case of a VTE. But so far there are no general guidelines for prevention of VTE with anticoagulants in the setting of MDS.

**Conclusion**

Lenalidomide is a promising target in both Multiple Myeloma and myelodysplastic syndromes. For patients with MDS treatment with lenalidomide improves quality of life significantly, mainly by reducing transfusion dependence. This seems to be most beneficial for patients carrying del5q, but nonetheless most probably for patients with other specific erythroid gene expression profiles. In patients with MM it offers new treatment options, so far mainly in patients with relapsed or refractory disease.

**Disclosure**

The authors report no conflicts of interest.

**References**


