Lenalidomide: a brief review of its therapeutic potential in myelodysplastic syndromes

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Abstract: Lenalidomide is a novel thalidomide analogue with enhanced immunomodulatory and antiangiogenic action lacking most of the typical thalidomide-associated adverse events. In myelodysplastic syndromes (MDS), it has been used primarily in the IPSS low- and intermediate-1 risk setting. Several trials have demonstrated its potential to lead to both erythroid and cytogenetic responses in these disease groups. In a clinical trial of patients with a del(5q) chromosomal abnormality, lenalidomide treatment resulted in red blood cell (RBC) transfusion independence in 67% of patients. Moreover, 45% of patients achieved a complete cytogenetic remission, and 28% achieved a minor cytogenetic remission. This result was independent of karyotype complexity. Lenalidomide might also induce long-term remissions in del(5q) patients with an elevated medullary blast count. In non-del(5q) patients, 43% of patients with confirmed low- and intermediate-1 risk achieved transfusion independence or a reduction of at least 50% of pre-treatment RBC transfusion levels. Adverse events are common but manageable and include neutropenia and thrombocytopenia, pruritus, rash, diarrhea, and others. Lenalidomide will prove an essential part in the armamentarium of MDS therapeutics. Combination therapies with cytokines, demethylating agents, tyrosine kinase inhibitors, or chemotherapy are being investigated and may show additional benefit in both low- and high risk MDS.

Keywords: Lenalidomide, myelodysplastic syndromes, therapy, clinical trials

Introduction

For many decades, the therapeutic approaches to myelodysplastic syndromes (MDS) have been a history of sorry failures. This was partly due to difficulties in diagnosis and prognostication, but also due to a poor understanding of the basic pathophysiology of MDS. Recent years have shed light on most of these issues (Aul et al 1998), and, consequently, led to the identification of possible cellular, immunological, and molecular therapeutic targets. Moreover, it has been recognized that the bone marrow microenvironment is not an innocent bystander in the malignant process, but may play a crucial role in the development and the support of neoplastic stem cells and their progeny (Estey 2004). Several lines of evidence support the view that the bone marrow stromal cells may be an independent target for therapeutic interventions in myelodysplatic syndromes, as they seem not to be derived from a common hematopoietic malignant marrow stem cell (Ramakrishnan et al 2006). Our current understanding of the pathogenic mechanisms in MDS is that genetic alterations within hematopoietic stem cells might confer a growth advantage to them (Aul et al 1998; Fenaux 2001). These mutational events may be point mutations or loss or gain of chromosomal material, and may be found in the genome of the cellular nucleus or be confined to the mitochondrial DNA (Greenberg et al 2002). Furthermore, epigenetic alterations may lead to silencing of DNA sequences that interfere with normal proliferation and differentiation (Lubbert 2003). The morphological correlates of these genetic abnormalities are dysplastic hematologic progenitors and effector cells in a

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hypercellular bone marrow of affected individuals (Schaefer and Lubbert 2005). Still, the disease is usually accompanied by peripheral pancytopenia. The paradox of bone marrow hypercellularity and peripheral cytopenia is explained by increased apoptosis in hematopoiesis that is partly due to an impaired responsiveness of progenitor cells to trophic signals and the generation of inhibitory cytokines by immune cells, bone marrow stroma, and malignant cells themselves (Aul et al 1998). At later stages of the disease, a shift from apoptosis to proliferation occurs (Parker and Mufti 1998) and about 30% of patients' bone marrows undergo evolution to acute myeloid leukemia (AML) (Heaney and Golde 1999).

Cytogenetic abnormalities in MDS

Abnormalities detected by conventional cytogenetics occur in 30 to 50% of *de novo* MDS and in 80 to 90% of secondary MDS patients (Solé et al 2005). In contrast to acute myeloid leukemias, chromosomal aberrations in MDS usually involve loss or gain of chromosomal material, thus suggesting that the loss of tumor suppressor genes or haploinsufficiency of genes necessary for normal myelopoiesis play a critical role in pathogenesis (Olney and Le Beau 2001). A recent analysis of 2124 patients from several MDS centers shows that the most common cytogenetic abnormalities in myelodysplastic syndromes involve deletion of the long arm of chromosome 5 [del(5q)] in about 15% of patients, chromosomal aberrations of chromosome 7 (10% of abnormalities), trisomy 8 (8% of cases), and complex karyotypes (13% of cases) (Haase et al 2005). Targeting specific chromosomal aberrations could therefore be of importance for a significant number of patients suffering from MDS.

Therapeutic strategies in MDS

Currently, the therapeutic decisions for myelodysplastic syndromes are usually based on the International Prognostic Scoring System (IPSS) proposed by Greenberg and co-workers (Greenberg et al 1997). This system includes number and degree of peripheral cytopenias, bone marrow blast count, and bone marrow cytogenetics to determine the overall survival and the probability of AML evolution in a given patient with MDS (Table 1). It is common clinical practice to group patients with low- and intermediate-1-risk- disease into one MDS risk category and intermediate-2 and high-risk patients into a higher risk group. If eligible, patients with high-risk MDS should undergo allogeneic bone marrow transplantation, because this treatment has shown a survival advantage over supportive care (Steensma and Bennett 2006). Patients with low-risk MDS (including IPSS low- and intermediate-1 risk) probably benefit from a more conservative approach, leaving allogeneic stem cell transplantation for the time of clinical progression of the disease (Cutler et al 2004). Different treatment options are summarized in Table 2 (Bowen et al 2003, Bowen 2005, Steensma and Bennett 2006). Most of these treatments are appropriate for subsets of patients. Erythropoietin (EPO) with or without granulocyte colony stimulating factor (G-CSF) is most efficacious in patients with low endogenous EPO levels and low red cell transfusion burden (Hellstrom-Lindberg et al 2003), while antithymocyte globulin and cyclosporine A seems to be promising in younger patients with a certain HLA subtype (DR B15) and hypoplastic MDS (Molldrem et al 2002). Epigenetic therapy with the demethylating agents azacitidine or decitabine may be used in patients with poor risk karyotypic abnormalities with int-1 disease (Lubbert and Wijermans 2005; Raj et al 2005). The immunomodulatory drug lenalidomide has yielded impressive results in the subset of red blood cell (RBC) transfusion dependent myelodysplastic syndromes with a del(5q) cytogenetic abnormaliy. The data of a phase II study led to its approval for this indication in December, 2005 (List et al 2005). Furthermore, lenalidomide

Table 1 The international prognostic scoring system (IPSS) (Greenberg et al 1997)

		Points				
		0	0.5	1	1.5	2.0
BM blasts (%)		0–4	5–10		11–20	21–29
Number of cytopenias[1]		0–1	2–3			
Cytogenetic category[2]		low	int	high		
Risk group	Score					
Low	0					
Intermediate I	0.5–1					
Intermediate II	1.5–2					
High	≥2.5					

[1]Neutrophils <1800/μl, platelets <100.000/μl, hemoglobin <10g/dl

[2]Good: normal, isolated del(5q), isolated del(20q), isolated –Y; poor: chromosome 7 abnormalities, complex abnormalities (⩾ chromosomal abnormalities); intermediate: all others.

Table 2 Current treatment options in low- and intermediate-1 risk myelodysplastic syndromes (not covering all experimental therapies)

- Blood transfusion (erythrocytes, platelets)
- Iron chelation therapy (deferasirox, deferoxamine, deferiprone)
- Danazol
- Pyridoxine
- Erythropoietin ± granulocyte colony-stimulating factor
- Valproic acid
- Antithymocyte Globulin and cyclosporine A
- Lenalidomide
- 5-Azacitidine
- Decitabine
- Low-dose cytarabine

has also been used in other low- and int-1-risk MDS leading to red cell transfusion independence in a significant number of patients (Raza et al 2005).

Lenalidomide: a pleiotropic thalidomide analogue

Lenalidomide is chemically closely related to its parent compound, thalidomide (Bartlett et al 2004). However, the structural alterations between those compounds have as consequence pronounced differences in biological effects, the most striking, perhaps, being that lenalidomide is non-teratogenic in the New Zealand rabbit preclinical model, which is the most sensitive animal model for thalidomide-associated teratogenicity (Bartlett et al 2004) (Table 3). In preclinical and clinical tests, lenalidomide was shown to have a wide range of immunomodulatory, anti-inflammatory, and antiangiogenic properties (Bartlett et al 2005). Angiogenesis is a complex process involving interactions between endothelial cells, extracellular matrix, soluble factors, and their receptors (Estey 2004). Potent proangiogenic factors are vascular endothelial growth factor (VEGF) (Leung et al 1989) and basic fibroblast growth factor (bFGF) (Crane and List 2005), the levels of which are significantly reduced in the presence of lenalidomide (Bartlett et al 2004). Interestingly, VEGF is not only a powerful proangiogenic molecule but also directly stimulates leukemia cell self-renewal, as those cells may excrete VEGF and express VEGF-receptors (Estey 2004). In del(5q) myelodysplastic syndromes, the levels of VEGF and its receptor KDR were significantly reduced in all complete responders to lenalidomide, and vascularization normalized, which proved to be a prognostic factor for remission induction and remission maintenance (Büsche et al 2005). In multiple myeloma, lenalidomide prevented growth by inhibiting plasma cell adhesion to bone marrow stromal cells (BMSCs) (Hideshima et al 2000). Adhesion of multiple myeloma cells to BMCSs triggers secretion of proangiogenic cytokines and further promotes angiogenesis (Bartlett et al 2004).

The anti-inflammatory effects of lenalidomide are based on its ability to reduce TNF-α production and inhibit Interleukin (IL)–6 and IL–1β-production, while enhancing IL–10, IL–2 and Interferon (IFN)-γ secretion (Corral et al 1999). Immune modulation was shown in both chronic viral infections, in animal models treated after Raji lymphoma cell inoculation, and in in-vitro models with anti-CD3-stimulated $CD4^+$ and $CD8^+$ T-cells during peripheral blood mononuclear cell co-stimulation (Mitsiades and Mitsiades 2004).

Clinical use of thalidomide in myelodysplastic syndromes

There is no doubt that thalidomide is an active compound in the treatment of myelodysplastic syndromes. A number of international study groups have investigated on the safety and efficacy of thalidomide in both low- and high-risk MDS patients. Raza et al (Raza et al 2001) treated 83 patients (36 refractory anemia, RA, 13 patients with refractory anemia with ring sideroblasts, RARS, 24 refractory anemia with blast excess, RAEB, 6 refractory anemia with blast excess in transformation,

Table 3 Comparison of clinical, biological, and molecular features between thalidomide and lenalidomide

	Thalidomide	Lenalidomide
Teratogenicity (animal model)	+	–
Inhibition of cytokine generation (TNF-α, IL-6)	+	+++
Stimulation of IL-10, IL-2, IFN-γ	+	+++
Antiangiogenesis	+	++
Adverse events		
Constipation	++	–
Polyneuropathy	++	–
Sedative effects	+++	–
Deep venous thrombosis	+	(+)*
T-cell costimulatory effect	+	++
Enhancement of NK-cell Cytotoxicity	+	+
Reduction in tumor growth in Vivo (SCID mice)	+	++

Abbreviation: NK, natural killer; IL, Interleukin; TNF, tumor necrosis factor; IFN, Interferon; SCID, severe combined immunodeficiency.
* DVT not a clinical problem in myelodysplastic syndromes, but important in multiple myeloma.

RAEB-t, and 4 patients with chronic myelomonocytic leukemia, CMML) at a median age of 67 years with doses ranging from 100 to 400 mg thalidomide per day. Only 8 patients took the maximum dose of 400 mg thalidomide throughout the study. The majority of patients did not tolerate higher doses than 150 to 200 mg once daily. 51 patients completed at least 12 weeks of therapy, the remaining 32 patients stopped study drug early due to adverse events or progressive disease. 16 out of 51 patients (31%) showed hematologic improvement, with 10 out of 51 patients (20%) achieving major responses according to IWG criteria (Cheson et al 2000), ie, transfusion independence in previously transfusion dependent patients. Median duration of responses was 306 days (range, 90–620). Interestingly, most of the responders belonged to the low- and intermediate-1-risk IPSS group (9 RA and 5 RARS). Responders had a significantly higher pretherapy platelet count than non-responders and a lower pretreatment transfusion dependence for platelets. No cytogenetic remissions were observed in this study, however, Strupp et al reported three cytogenetic responses out of 16 MDS patients with chromosomal abnormalities treated with thalidomide (Strupp et al 2003). Two of the three patients were poor risk karyotypes (RA, 45, XY, –7, and RAEBt, complex karyotype), but most importantly, two of these patients had involvement of the long arm of chromosome 5; one as a single abnormality (RA, 46, XX, del(5)(q22q33), and one as part of a complex karyotypic abnormality [RAEBt, 46, XY, del(2)(p13?4), del(5)(q13q33), add(17)(p11), del(20)(q11)]. These patients were included in a report of a trial of 53 patients with MDS treated with thalidomide for myelodysplastic syndromes: 22 RA, 9 RARS, 6 RAEB, 12 RAEBt, 4 CMML, median age 66 years. Median thalidomide dosage was 300 mg. 22 out of 53 patients discontinued thalidomide because of adverse events. The overall response rate according to IWG criteria was 26 out of 53 patients, ie, 49% at a median follow-up of 12 months (range, 12 to 25 months) (Musto 2004).

Two other studies confirmed the activity of thalidomide in MDS patients, with overall responses ranging from 20 to 38 % (Musto 2004).

Clinical use of lenalidomide in myelodysplastic syndromes

Given the successful clinical use of thalidomide in myelodysplastic syndromes and the fact that lenalidomide has significantly stronger antiangiogenic and anticytokine properties than the parent compound, clinical trials investigating the potential of this immunomodulatory drug (IMiD®) in the treatment of MDS have consequently been designed. The trials focused mainly on transfusion-dependent low- and intermediate-1 risk MDS populations, although clinical trials in high-risk MDS and AML patients are also currently being performed.

Lenalidomide (CC5013)-MDS-001 trial

In the Lenalidomide- MDS-001 trial, List and co-workers treated 43 patients with MDS and transfusion-dependent or symptomatic anemia with varying doses of oral lenalidomide, ranging from 25 mg every day to 10 mg daily to 10 mg for 21 days of every 28 days cycle (List et al 2005). All patients had had no response to erythropoietin therapy or had high endogenous erythropoietin level with low probability of benefit to such therapy. Responses were defined according to the modified IWG criteria (Cheson et al 2000). A major erythroid response was defined as freedom from transfusion or an increase in hemoglobin levels of more than 2 g/dl in previously transfusion dependent patients. A major cytogenetic response was defined by the absence of the prestudy cytogenetic abnormality in at least 20 metaphases, a minor response by a reduction of at least 50% in the number of abnormal metaphases. 43 patients were included with a median age of 72 years (range, 28–85). 20 patients (47%) had RA, 13 patients (30%) RARS, 8 patients RAEB (19%), 1 patient RAEBt (2%), and 1 patient CMML (2%). 88% of patients had low- or int-1 risk IPSS risk assessment. 74% of patients were transfusion dependent with a median transfusion requirement of 3 packed red cells every 4 weeks. 53% of patients had an abnormal karyotype, 47% had no chromosomal abnormalities.

Lenalidomide-MDS-001 trial – Patient sample at a glance

- About 75% of patients heavily transfusion dependent.
- Representative study population regarding age and sex distribution of patients.
- 88% of patients low- or intermediate-1 risk according to IPSS.
- Abnormal karyotypes in about 50% (Table 4).

Fiftysix percent of patients (n = 24) had a response to lenalidomide treatment. 63% of transfusion-dependent patients (20 out of 32) achieved transfusion independence. The median hemoglobin increase in major responders (ie, reaching transfusion independence or >2 g/dl increase in

Table 4 Lenalidomide-MDS-001 trial – Chromosomal abnormalities and responses at a glance (List et al 2005)

Cytogenetic abnormality	No. of patients	Complete cyto genetic responses
del(5q31.1)	12	9(75%)
isolated	11	8
with trisomy 21	1	1
del(20)(q11.2)	2	0
T(1;22)(q21p11.2)	1	1
Other*	5	0
Total	20	10(50%)

*+19; +8; –X; t(3;3) (q21; q26.3); and complex

hemoglobin) was 5.3 g/dl. 1 out of 10 patients with moderate to severe thrombocytopenia had a sustained platelet count increase, 2 out of 12 patients with severe neutropenia had a sustained neutrophil increase. The only significant predictive factor for response was the karyotypic abnormality at treatment onset. 83% of patients with a del(5q31) MDS had a response as compared to 53% of patients with a normal karyotype and 12% of patients with other karyotypic abnormalities (Table 5). The most common adverse events were neutropenia and thrombocytopenia and necessitated dose interruption or dose reduction in 58% of patients, and this was dose dependent (77% in the 25 mg group, 62% in the 10 mg daily group, and 47% in the 10 mg 3 weeks out of 4 group, see Table 6). Other adverse events, albeit not usually of grade 3 and 4 according to National Cancer Institute (NCI) were pruritus, urticaria and skin rash, diarrhea, hypothyroidism and hypogonadism.

Table 5 Predictive factors for lenalidomide response at a glance (Lenalidomide-MDS-001 trial, total number of patients, n=43) (List et al 2005)

Variable	No. of patients	Erythroid response (%)	P-value
IPSS risk group			0.14
Low	22	15 (68)	
Intermediate-1	16	8 (50)	
Intermediate 2 or high	5	1 (20)	
FAB classification			0.07
RA	20	15 (75)	
RARS	13	6 (46)	
RAEB(t)	9	3 (33)	
CMML	1	0	
Karyotype			0.007
del(5q31)	12	10 (83)	
Normal	23	13 (57)	
Other	8	1 (12)	

Four patients had transient emergence of karyotypically unrelated clones. Sustained acquisition of chromosomal aberrations occurred in four patients. Three del(5q31) patients developed chromosome 7 abnormalities and one patient with a normal pre-treatment karyotype developed del(20q). One of these four patients had exacerbation of anemia at the time of emergence of chromosomal abnormality. This patient transformed into acute leukemia. The other patients remained transfusion free.

Conclusion of the Lenalidomide-MDS- 001 trial

This trial clearly showed the potential of lenalidomide in the treatment of myelodysplastic syndromes. Patients with a del(5q31) chromosomal aberration appeared to be responding especially well to treatment. Neutropenia and thrombocytopenia were common side effects. Thrombocytopenia is a less important clinical problem, though. 54% of patients experienced grade 3 or 4 thrombocytopenia, but grade 4 is the clinical important problem (platelets <25,000/μl), while grade 3 does not usually lead to spontaneous bleeding. The typical adverse events reported with thalidomide (eg, constipation, fatigue, polyneuropathy) were uncommon or non-existent. The significance of sustained acquisition of chromosomal abnormalities is unclear, three out of four patients with emergence of new clones were sustained responders to the drug.

Given that the MDS-001 trial had shown different efficacy in MDS patients with del(5q31) cytogenetic abnormality and non-del(5q) MDS, two further trials were designed to study the effects of lenalidomide in more depth in those study populations. The MDS 003 trial was designed for transfusion dependent del(5q) MDS patients, the MDS 002 trial for patients with other or no chromosomal abnormalities.

Lenalidomide (CC5013)-MDS-002 trial (Raza et al 2005)

In this clinical phase II study, transfusion-dependent MDS patients needing at least 2 RBC concentrates every 8 weeks were included. Patients were eligible if they had low- or intermediate-1 risk MDS without any or with non-del(5q) chromosomal abnormalities. Because of the myelosuppressive effect demonstrated by lenalidomide the patients were to have >50,000/μl platelets and an absolute neutrophil count (ANC) of >500/μl. The primary endpoint of the study was transfusion independence; secondary endpoints included cytogenetic and pathologic response to lenalidomide. This trial has not yet been published as a full paper, which limits the definite data

Table 6 Hematological adverse events at a glance (Lenalidomide-001-trial, total number of patients, n = 43) (List et al 2005)

	Grade 1 or 2 (NCI)	Grade 3 or 4 (NCI)	All patients, all grades
Neutropenia	0	28 (65%)	28 (65%)
Thrombocytopenia	9 (21%)	23 (53%)	32 (74%)

analysis. 215 patients at a median age of 71 years were included in this trial. 77% of evaluable patients had a normal karyotype, 23% displayed chromosomal abnormalities. Low- and intermediate-1 risk MDS was confirmed in 79% of patients. Average duration of MDS was 2.7 years (range, 0.1–12.9 years). In the intent-to-treat analysis including all 215 patients regardless of central review eligibility, 21.4% were identified as transfusion independent with a median haemoglobin rise of 3.0 g/dl. Among 79% low- and intermediate-1 patients 25% became transfusion independent, while a total of 43% achieved a major or minor response (Table 7). The median time to transfusion independence was 4.2 weeks. The duration of response was at least 24 weeks in 17% of responders and was at least 52 weeks in 10% of the patients. As in the MDS 001 trial, the most common adverse events were neutropenia and thrombocytopenia (Table 8). These adverse events necessitated treatment interruption in 19% and 15%, respectively. Possible drug related deaths were reported in 2% of patients. Those were due to neutropenic infections.

Lenalidomide-MDS-002 trial – Patient sample at a glance

- Representative MDS study population regarding age and sex distribution of patients.
- 80% of patients low- or intermediate-1 risk according to IPSS.
- Normal karyotypes in 77%.

Conclusion of the Lenalidomide-MDS-002 trial

Lenalidomide unequivocally has erythroid remitting activity in myelodysplastic syndromes, not only in the del(5q) population but also in patients with normal or other abnormal karyotypes. Neutropenia and thrombocytopenia were the most common side effects, however, in the non-del(5q) population these adverse events are about half as frequent as in del(5q) MDS patients. The study shows a 43% overall erythroid response rate in the low- and intermediate-1 risk patients. This included minor erythroid responses with a 50% reduction in transfusion requirements compared to baseline, which is a rather weak response criterion. However, 25% of patients achieved transfusion independence with a median hemoglobin rise of 3.0 g/dl, comparing favorably to many other therapies in this indication. This trial included 77% of patients with a normal karyotype. Additional studies are needed in non-del(5q) patients with other karyotypic abnormalities to assess lenalidomide's ability to induce erythroid responses in these patient subgroups.

Table 7 Responses in Lenalidomide-MDS-002 trial (Raza et al 2005)

Intent to treat (n = 215)	No. of patients (%)
Transfusion Independence	21.4%
Low-/Intermediate-1 patients (n = 169)	
Transfusion Independence	25%
Minor response	18%
(>50% reduction of transfusion requirements)	
Total	43%

Lenalidomide MDS-003-trial

The very impressive results of the Lenalidomide-MDS-001 trial prompted the design of an international phase II trial for patients with a del(5q) chromosomal abnormality, the results of which have recently been reported in the New England Journal of Medicine (List et al 2006). The study population consisted of 148 transfusion-dependent patients (>2 RBC/ 8 weeks, median RBC transfusion burden 6 Units/8 weeks) with a median age of 71 years and a female preponderance typical of the 5q-syndrome. Mean MDS duration at study enrolment was 3.4 years (<0.1 to 20.7). The patient population consisted of transfusion-dependent low- and intermediate-1-risk MDS patients according to IPSS with a del(5q) cytogenetic abnormality including bands q31–q33, allowing for the inclusion of patients with del(5q) chromosomal abnormalities plus one or more other cytogenetic aberrations, as well as patients with a medullary blast count of >5%. It is important to recognize that these different patient populations, although sharing the del(5q) chromosomal abnormality, have a very different overall survival. In fact, while patients with an isolated del(5q) aberration and a normal bone marrow blast count (the 5q-syndrome) have a median overall survival exceeding 6 years (Giagounidis et al 2004), this figure shrinks to 48 months for patients with one additional chromosomal aberration (eg, del(5q) +21), and more so for patients with complex karyo-

Table 8 Hematological adverse events leading to treatment interruption in the Lenalidomide-MDS-002-trial (Total number of patients, n = 215) (Raza et al 2005)

	All patients, all grades
Neutropenia	19%
Thrombocytopenia	15%

types including del(5q) (median overall survival 7–8 months (Giagounidis et al 2005)). An increase in bone marrow blasts in patients with an isolated del(5q) abnormality also confers a worse prognosis compared to the 5q-syndrome, those patients having a median overall survival of about 2 years (Giagounidis et al 2004). By choosing the above-mentioned inclusion criteria, the Lenalidomide-MDS-003 trial was able to address the question of whether this compound was able to act not only on the 5q-syndrome population, but also on higher-risk disease subgroups.

Lenalidomide-MDS-003 trial – Patient sample at a glance

- Transfusion-dependent del(5q) MDS patients of low-and intermediate-1 IPSS risk.
- Representative del(5q) study population regarding age and sex distribution of patients.
- Additional karyotypic abnormalities allowed.
- Increased medullary blast count up to 10% allowed if isolated del(5q).
- Platelet count >50,000/μl and ANC >500/μl required.

Primary endpoints in this trial, as in the MDS 002 trial, were transfusion independence, secondary end points were cytogenetic and pathological response. To be classified as a major response, transfusion independence had to last for at least 8 weeks and be accompanied by a rise in hemoglobin of at least 1 g/dl. Lenalidomide was given at 10 mg/day with possible dose reductions in case of adverse events to 5 mg p.o. daily and 5 mg p.o. daily every other day. Response according to modified IWG criteria (Cheson et al 2000) was assessed after 24 weeks. Among 148 included patients, 111 had a single del(5q) chromosomal abnormality, and 37 patients had additional chromosomal abnormalities. Central cytology and cytogentic review was performed and 120 patients (81%) confirmed as suffering from low/ intermediate-1 risk MDS. The intent-to-treat analysis showed that 67% of patients (95% confidence interval 59%–74%) became transfusion free, defined as ≥56 days of transfusion independence and a ≥1 g/dl rise in hemoglobin (Table 9). The median increase in hemoglobin from baseline to the maximum hemoglobin achieved during RBC transfusion independence was 5.4 g/dl and the median interval to response was 4.6 weeks. 90% of patients who achieved a transfusion benefit did so by completion of three months in the study. RBC transfusion independence were unaffected by age, gender, FAB type, IPSS category or cytogenetic pattern. However, the patient numbers in intermediate-2 and high risk IPSS were very low (6 and 2, respectively). With a median follow-up of 104 weeks, the median duration of transfusion-independence was not reached. Although patients with isolated del(5q) were more likely to achieve transfusion independence (72%), 48% of patients with one additional chromosomal abnormality and 67% of those with 2 or more additional abnormalities did also achieve freedom from transfusion. 73% of patients achieved a cytogenetic response: 45% had a complete cytogenetic remission with absence of the del(5q) cytogenetic abnormality in follow-up karyotyping, and 28% had a reduction of at least 50% in abnormal metaphases (Table 9). 23 patients acquired new chromosomal abnormalities during lenalidomide treatment, 10 of whom were cytogenetic responders. 84% of patients had to interrupt the dose of lenalidomide due to adverse events at least once. The median time to the first dose interruption or reduction was 22 days. The median duration of the first interruption was 22 days. A second dose reduction or interruption was necessary in 33.8% of patients. This second interruption had a median duration of 21 days. Grade 3 or 4 neutropenia developed in 55% of patients, grade 3 or 4 thrombocytopenia in 44% (Table 10). Nine patients progressed to higher MDS subtypes or acute myeloid leukemia, and 11 patients died due to disease complications (n = 8) or neutropenic infection (n = 3).

Conclusion of the Lenalidomide-MDS-003 trial

Lenalidomide is a highly effective treatment for patients with a del(5q) myelodysplastic syndrome. 67% of patients in this trial became transfusion independent with a median hae-

Table 9 Lenalidomide-MDS-003: Erythroid and cytogenetic response rates (List et al 2006)

Intent to treat (n = 148)	No. of patients (%)
Transfusion Independence	99 (67%)
>50% reduction of transfusion need (but not transfusion-free)	13 (9%)
Median haemoglobin increase	5.4 g/dl
Median interval to response	4.6 weeks
Overall cytogenetic response	73%
Complete cytogenetic response	45%

Table 10 Lenalidomide-MDS-003: Overview on hematological adverse events (List et al 2006)

Intent to treat (n = 148)	No. of patients (%)
Neutropenia (Grade 3 or 4)	55%
Thrombocytopenia (Grade 3 or 4)	44%
Median duration of treatment interruptions	3 weeks

moglobin rise of 5.4 g/dl. The median duration of response has not been reached at the latest data cut-off. Importantly, the drug's cytogenetic remitting activity is not confined to patients with isolated del(5q), but also occurs in patients with additional chromosomal abnormalities. Neutropenia and thrombocytopenia are the most common side effects, occurring in 55% and 44% of patients.

Conclusion and future perspectives

It may turn out to be a fortunate event that thalidomide, a sedative once developed by Chemie Grünenthal in Germany in the 1950s, did not disappear completely from the pharmaceutical market after the shocking and traumatizing teratogenic effects that struck thousands of families during the early years of its marketing. Indeed, it seems to be by complete chance that the beneficial effects of thalidomide on *Erythema nodosum leprosum* were discovered by Jacob Sheskin in 1965 (Sheskin 1965). More than thirty years later, chance again led to the discovery of thalidomide's positive action in multiple myeloma (Singhal et al 1999). Since, extensive research has discovered a number of thalidomide analogues with augmented immunomodulatory and anti-cytokine effects that may lead to important steps forward in the treatment of neoplastic diseases. In multiple myeloma and in the myelodysplastic syndromes, this has already been achieved by one of those new compounds, namely CC5013, or lenalidomide. In MDS, past and current trials have unequivocally shown that this drug has a potential to alleviate transfusion dependence in all subgroups of MDS. It seems to be particularly effective in patients with a del(5q) chromosomal abnormality when the bands q31 to q33 are involved. Here, this drug has shown to achieve transfusion independence in the majority of patients with isolated del(5q) or additional chromosomal abnormalities. The MDS-002 and 003 trials were designed to study low- and intermediate-1 patients. This led to the opportunity to study whether the drug is able to reduce a significantly elevated blast count, too. It turns out that lenalidomide not only may restore a normal erythropoiesis in del(5q) patients, but that it may also decrease an elevated blast count to normal ranges. It is at present unclear whether treatment with lenalidomide alone is sufficient to induce long-term remissions in patients with elevated blasts or whether some form of combination treatment may be necessary to provide sustained response. In those patients with a del(5q) and a normal medullary blast percentage, however, it is clear that monotherapy with lenalidomide may lead to long-term transfusion independence for at least several years. Furthermore, among patients with a del(5q) chromosomal aberration, those with two or more chromosomal aberrations, ie, a complex karyotype, undoubtedly do have an ominous prognosis (Giagounidis et al 2005). Lenalidomide is able to induce long term hematologic and cytogenetic remissions in these patients with low- and intermediate-1 IPSS risk (Giagounidis et al 2006, Giagounidis et al 2005) and very probably alters the natural course of the disease in this patient population. Whether, in analogy, this is also true for patients with isolated del(5q) or with one additional karyotypic abnormality is unclear at the moment. The drug definitely improves quality of life in responding patients. Patients not responding to the drug during active treatment periods may experience a sustained rise in hemoglobin after drug discontinuation (Giagounidis et al 2006). Also, in our experience, patients interrupting treatment after short courses of lenalidomide (4–6 weeks) may experience prolonged transfusion independence of >18 months (Giagounidis et al 2006). A number of patients will lose their response to the drug during active treatment. Some of these patients may be salvaged with readministration of the initial dose of lenalidomide (10 mg) after a drug holiday of 4 weeks to 6 months. It has become clear that del(5q) patients are especially prone to hematologic toxicity after lenalidomide administration. To prevent neutropenia, granulocyte colony-stimulating factors should be administered early at onset of neutropenia. Especially during the first 8 weeks of treatment, full blood counts must be checked weekly to avoid serious hematologic side effects and possibly lethal complications of neutropenia. If the drug is interrupted at 30–50.000/µl platelets, the probability of severe bleeding is minimal, and never happened in our personal experience. The question has arisen whether it would be feasible to treat patients through the neutropenia and thrombocytopenia with vigorous supportive care, hoping to achieve higher response rates by administering a higher cumulated lenalidomide dose. However, given that patients with low- and intermediate-1 risk disease according to the IPSS have median survival rates of 3.5 to >5 years, and that the survival of 5q-syndrome patients does exceed those figures, ethical considerations have led to a reluctance regarding this approach. As long as more mature data from clinical trials are missing, we feel that treatment interruption should be

performed according to the guidelines outlined in the studies reported on. Lenalidomide is a thalidomide analogue. Every precaution must be taken to prevent pregnancies during and for at least one month after lenalidomide intake.

Whether the combination of erythropoietin and lenalidomide will be able to improve overall responses is uncertain. Given that erythropoietin levels in del(5q) patients are usually very high at the time of diagnosis (Giagounidis et al 2004), it is improbable that a combination therapy will improve responses significantly. Also, the drug's potential in advanced MDS or AML with del(5q) requires further studies. Firstly, those diseases may have a different genetic basis than low-risk MDS with del(5q) because the critical deleted region on chromosome 5 is likely to be different (Boultwood et al 2002). Secondly, although lenalidomide *in vitro* has got a direct apoptotic effect on del(5q) cells, its action is usually considered more from an immunomodulatory, anti-cytokine, and bone marrow microenvironment balancing view. In this case it is improbable that lenalidomide alone will cure patients with an elevated blast count >10%, but it may be an important adjunct to other drugs, including conventional chemotherapy, demethylating agents, farnesyl transferase inhibitors, tyrosine kinase inhibitors, and others.

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