Horizon Scanning in Oncology

Lenalidomide (Revlimid®) for the treatment of low /intermediate-1 risk myelodysplastic syndrome with chromosome 5q deletion

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DSD: Horizon Scanning in Oncology Nr. 28
ISSN online 2076-5940

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Vienna, May 2012

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft in collaboration with Azienda Ospedaliera Universitaria Integrate Verona (UVEF; Italy) and with Agencja Oceny Technologii Medycznych (AOTM; Poland)

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This product of collaboration with UVEF and with AOTM an offspring of the European network for Health Technology Assessment (EUnetHTA) Project that was supported by a grant from the European Commission. The sole responsibility lies with the author(s), and the Commission is not responsible for any use that may be made of the information contained therein.

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Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

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1 Drug description

Generic/Brand name/ATC code: Lenalidomide/Revlimid®/ L04 AX04

Developer/Company: Celgene Europe Limited

Description: Lenalidomide is a second generation immune-modulatory agent with several modes of action, inducing anti-neoplastic, anti-angiogenic, pro-erythropoietic and immune-modulatory effects. These effects are exerted by inhibition of TNF-α production, activation of T cells and by reduction of serum levels of the cytokines vascular endothelial growth factor and basic fibroblast growth factor [1, 2].

lenalidomide is an immune-modulatory agent with anti-neoplastic, anti-angiogenic, pro-erythropoietic effects

Revlimid® capsules are available at different dosages: 2.5 mg, 5 mg, 10 mg, 15 mg and 25 mg. For myelodysplastic syndromes (MDS), the recommended daily dose is 10mg orally. It has to be noted though, that the optimal dosage has not been confirmed irrevocably since lower dosages have also shown activity [3]. In addition while the current recommendation is to administer lenalidomide until relapse of transfusion dependence, progression of disease or occurrence of intolerable side-effects [4], interruption of therapy 6 months after complete cytogenetic remission might reduce costs and side-effects while simultaneously achieving prolonged transfusion independence (TI) [4].

10mg daily orally

Due to the fact that neutropenia and thrombocytopenia are often the most serious side-effects of lenalidomide, complete blood counts should be performed weekly for the first 8 weeks and monthly thereafter in MDS patients treated with this drug. Dose reductions or even interruption of treatment is necessary if neutropenia or thrombocytopenia develops. Other, serious adverse events possible are deep venous thrombosis and pulmonary embolism, but if prophylactic use of anticoagulation or antiplatelet therapy is indicated has to be determined based on the individual patient's medical record [5]. Special caution is required in females patients of childbearing age, because lenalidomide causes foetal harm at all doses [5].

adverse events: neutropenia, thrombocytopenia, deep venous thrombosis, pulmonary embolism

2 Indication

Lenalidomide for the treatment of red blood cell (RBC) transfusion-dependent patients with low- or intermediate-1-risk MDS associated with a deletion 5q (del(5q)) cytogenetic abnormality.

for low/intermediate 1 risk MDS + del(5q)

3 Current regulatory status

not licensed for MDS in Europe but for multiple myeloma

In Europe, lenalidomide is not licensed for the treatment of MDS, but the EMA granted market authorization for lenalidomide for

- the treatment of multiple myeloma in 2007.

Orphan drug designation was assigned for multiple myeloma in 2003, for myelodysplastic syndromes in 2004, for chronic lymphocytic leukaemia in 2007, and for mantle cell lymphoma and diffuse large B-cell lymphoma in 2011 [6].

in the US, licensed for MDS since 2005 but only under special risk evaluation programme

In the U.S., lenalidomide is an orphan drug, only available within the RevAssist® Programme, a risk evaluation and mitigation strategy with the aims of informing on the serious risks and safe-use conditions for Revlimid® and to prevent the risk of foetal exposure to the drug. The Food and Drug Administration (FDA) granted market authorisation for Revlimid® for [5]:

- patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) abnormality with or without additional cytogenetic abnormalities in December 2005.
- multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy in June 2006.

4 Burden of disease

MDS caused by genetic changes in haematopoietic precursor cells

MDS are caused by genetic changes in haematopoietic precursor cells in the bone marrow. MDS might develop de-novo or as a secondary MDS after chemotherapy or radiation therapy for other diseases [7]. The inability of the bone marrow to produce mature blood cells results in cytopenia of one or more of the peripheral blood cells and in an increasing number of bone marrow blast cells – factors which relate directly to the prognosis [8]. Symptoms include anaemia - the most common cytopenia which occurs in more than 90% of patients - repeated infections or bleeding [9]. About one third of patients suffering from MDS progress to acute myeloid leukaemia (AML)[8], which is often refractory to standard treatment [7].

IPSS system differentiates four risk groups

By reasons that MDS comprise a heterogeneous group of conditions, different classification schemes mainly based on the cellular morphology are in use, such as the French-American-British Classification (FAB) or the WHO classification [7]. To assess the individual risk at diagnosis, the International Prognostic Scoring System (IPSS) discriminates four risk groups. Based on number of cytopenia, percentage of marrow blasts and karyotype (i.e. chromosomal characteristics of a cell) different prognoses for survival and transformation to AML can be made for each risk-group [8]. According to the IPSS, median survival (without therapy) ranges from 0.4 years to 5.7 years [10]. Patients in low or intermediate-1 risk category have an estimated median survival of 5.7 and 3.5 years respectively.

median survival: 5.7 – 3.5 years for low/intermediate-1 risk

Depending on the type of chromosomal abnormalities, the IPSS differentiates between "good", "intermediate" and "poor" karyotypes. About 40-70% of patients show cytogenetic abnormalities, such as del(5q), -7 or del(7q), trisomy 8, del(20q), and loss of the Y chromosome [3]. Deletion of the long arm of chromosome 5 (del(5q)), the most common abnormality in MDS, is found in about 15% of patients. If there are no abnormalities, loss of the Y chromosome only or a del(5q) or del(20q) alone, the karyotype is rated as "good". In contrast, complex abnormalities (i.e. ≥3) or chromosome 7 anomalies determine poor karyotypes, whereas "intermediate" refers to all other abnormalities [8]. As reflected by the IPSS, MDS with del(5q) only have a relative good prognosis. If patients have an isolated del(5q) in addition to anaemia, normal or elevated platelet counts and fewer than 5% of blasts (i.e. immature precursor cells) in the bone marrow, this is referred to as 5q- syndrome [1, 8], a distinctive type of MDS mainly affecting older women (females vs males: 7:3) [3]. However, outcomes even of patients with del(5q) differ to a great extent. Additional chromosomal abnormalities seem to be prognostic factors for risk of AML progression and overall survival, leading to three risk categories for AML transformation (del(5q), del(5q)+1 and del(5q)+ ≥ 2 abnormalities) and two for OS (one group: del(5q) and del(5q)+1; and del(5q)+ ≥ 2 abnormalities, as the other one) [11]. Other factors which are discussed as being associated with an increased risk of AML transformation are a high risk WHO adapted Prognostic Scoring System score, a marrow blast count of >5% and red-blood cell transfusion dependency at diagnosis [12].

chromosomal abnormalities determine different karyotypes and thus prognosis

del(5q) related with good prognosis

No data are available on the overall incidence of MDS in Austria, but estimates from other countries range from 3.3 [13] to 5 per 100,000 people [14]. Applied to an Austrian population of 8,400,000 [15], an estimated 277 to 420 persons would be affected. Assuming a frequency of del(5q) of 15%, approximately 40 - 60 patients are newly diagnosed in Austria each year. The median age of diagnosis is about 70 to 75 years [13] with 90% of patients aged over 60 at time of diagnosis. In individuals over 70 years the incidence rises to between 22 and 45 per 100,000 population [8]It is thus likely that this number will increase in the future due to the increasingly elderly stratum of the population [16].

in Austria: approximately 40-60 patients newly diagnosed with del(5q) MDS/year

5 Current treatment

Asymptomatic patients with low-/intermediate-1-risk MDS do not require therapy, but should be monitored closely.

asymptomatic patients: monitoring

For symptomatic patients, no standard therapy exists and enrolment in clinical trials is highly recommended. Choice of therapy is influenced by patient's performance status and disease characteristics such as cytopenias present, serum erythropoietin level and probability of responding to immunosuppressive therapy.

symptomatic patients: enrolment in clinical trials recommended

therapy:

Generally, treatment approaches for patients with low-/intermediate-1-risk MDS are supportive care and low intensity therapies, aiming at improving quality-of-life, reduction of symptoms caused by cytopenias and avoidance of toxic therapies.

best supportive care,

- Supportive care: including antibiotics, red blood and platelet transfusions [3, 8] and iron chelation therapy (for patients which develop iron overload due to repeated blood cell transfusions).

  Supportive care is part of therapy for all MDS patients, but limiting therapy to supportive measures only, is indicated in frail older people with comorbidities [3, 17].

low intensity therapies, including erytropoietin, growth factors, azacitidine or lenalidomide

- Low intensity therapies: include the erythropoiesis stimulating agents (ESAs) erythropoietin or darbepoetin, growth factors (i.e. granulocyte colony stimulating factor (G-CSF)), DNA hypomethylating agents (i.e. azacitidine or decitabine) which are neither licensed nor recommended for low-risk MDS in Austria [17], immunosuppressive therapy (e.g. antithymocyte globulin and cyclosporine) for selected fit and younger patients and lenalidomide.
  - For patients with symptomatic anaemia, a serum erythropoietin level ≤500 mU/mL and without cytogenetic abnormalities, erythropoietin ± G-CSF is the preferred therapy.
  - Patients with symptomatic anaemia, with del(5q) ±other cytogenetic abnormalities and without clinically significant decreased neutrophils or platelets lenalidomide is considered as standard therapy, at least in the U.S. [3, 16-19].
  - Patients with symptomatic anaemia, a serum erythropoietin level >500 mU/mL, and a good probability of responding to immunosuppressive therapy (e.g. ≤60 years, hypocellular marrows), might be treated with antithymocyte globulin plus cyclosporine.
  - For patients with symptomatic anaemia, a serum erythropoietin level >500 mU/mL, who are unlikely to respond to immunosuppressive therapy and for patients with symptomatic thrombocytopenia or symptomatic neutropenia, hypomethylating agents and lenalidomide might be used [3, 17, 18].

    However, the majority of these regimens are considered as "experimental" and are not licensed for low/intermediate-1 risk MDS in Europe [17].

only curative therapy stem cell transplantation

The only curative therapy for MDS is stem cell transplantation, a therapy which is, like intensive chemotherapy, usually restricted to patients with high-risk MDS.

6 Evidence

A literature search was conducted on the 17th of February in 4 databases (Ovid Medline, Embase, Cochrane Library, CRD Database) yielding 198 results. Considered were phase III and phase II studies, compassionate-use programmes and other relevant study designs which have been fully published. Excluded were case-reports.

Overall 8 references were included [20-27], comprising 1 phase III study [20], 1 phase II study with long-term results [21, 22], a compassionate use programme [23, 27], an open-label study [24], data from post-marketing surveillance database [25] and a cost-effectiveness analysis [26].

8 references included

1 phase III

others: phase II, compassionate-use programme, post-marketing surveillance data

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title A randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del(5q) [20]		
Study identifier	NCT00179621, CC-5013-MDS-004, 2005-000454-73	
Design	Phase 3, multicentre (37 centres), randomized, double-blind, placebo-controlled Cross-over was allowed in the open label extension phase for patients in the lenalidomide 5 mg or in the placebo group	
	Duration	Enrolment: July 2005 to June 2007 Median follow-up: 1.5 years Cut-off date for final analysis: June 2008 Open-label extension phases: Patients without minor erythroid response by week 16 were discontinued from the double-blind phase, unblinded, and eligible for open-label treatment. Those completing the double-blind phase without disease progression or erythroid relapse were unblinded and could start open-label treatment at their current lenalidomide dose for up to 156 weeks.
Hypothesis	Superiority Assuming response rates (RBC-TI for 26 weeks) of 0.400 and 0.100 in the active and placebo groups, respectively, a sample size of 45 patients per group (mITT population) and a 2-group continuity corrected $\lambda 2$ test with a 0.025 2-sided significance level (α split to adjust multiple comparisons) has an 80% power to detect differences between each active treatment group and placebo.	
Funding	Celgene Corporation	
Treatment groups	Intervention 1	Randomised/mITT: n= 69/41 lenalidomide 10 mg/day on days 1 to 21 Duration: patients with at least a minor erythroid response (i.e. 50% decrease in transfusion requirements) by week 16 could continue double-blind treatment for up to 52 weeks or until erythroid relapse, disease progression, or unacceptable toxicity. Open-label therapy was offered for a maximum of 156 weeks to patients without disease progression or erythroid relapse.

	Intervention 2	Randomised/mITT: n= 69/47 lenalidomide 5 mg/day on days 1 to 28 Duration: patients with at least a minor erythroid response (i.e. 50% decrease in transfusion requirements) by week 16 could continue double-blind treatment for up to 52 weeks or until erythroid relapse, disease progression, or unacceptable toxicity. Open-label therapy was offered for a maximum of 156 weeks to patients without disease progression or erythroid relapse. Patients in the 5mg group without minor erythroid response by week 16 or those who had an erythroid relapse could-cross over to 10mg open-label extension phase.	
	Control	Randomised/mITT: n= 67/51 placebo on days 1 to 28 Duration: patients with at least a minor erythroid response (i.e. 50% decrease in transfusion requirements) by week 16 could continue double-blind treatment for up to 52 weeks or until erythroid relapse, disease progression, or unacceptable toxicity. Patients without minor erythroid response by week 16 or those who had an erythroid relapse could-cross over to 5mg or 10mg open-label extension phase.	
Endpoints and definitions	Red blood cell transfusion independence	RBC-TI	Red blood cell transfusion independence for ≥26 consecutive weeks
	Erythroid response	-	<u>IWG 2000 criteria [9]:</u> Response must last at least 8 weeks: Major response: for RBC transfusion-dependent patients, TI. Minor response: for RBC transfusion-dependent patients, 50% decrease in transfusion requirements. <u>IWG 2006 criteria [28]:</u> Response must last at least 8 weeks: For patients with pre-treatment haemoglobin less than 11 g/dL: Hgb increase by ≥ 1.5 g/dL; relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pre-treatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pre-treatment will count in the RBC transfusion response evaluation.
	Duration of RBC-TI	-	Number of days between the last transfusion before the start of the TI period or the first dose of lenalidomide, whichever occurred later, and the first transfusion after the TI period (according to IWG 2000 criteria)
	Cytogenetic response	CR	According to IWG 2000 criteria and determined based on karyotyping results [9] (requires 20 analysable metaphases using conventional cytogenetic techniques: Major response: No detectable cytogenetic abnormality, if pre-existing abnormality was present. Minor response: 50% or more reduction in abnormal metaphases)
	Overall survival	OS	Time from randomization to death from any cause
	Time to acute myeloid leukaemia progression	-	Time from randomisation to diagnosis of AML (French-American-British criteria)
	Health-related quality of life	HRQoL	Assessed using the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire

Results and analysis					
Analysis description	Modified intent-to-treat (mITT) population was used to assess efficacy and included patients with centrally confirmed Low- or Intermediate-1-risk MDS with del(5q31) and documented RBC transfusion dependence, who received ≥ 1 dose of study drug. ITT population included randomised patients, safety analysis those who received ≥1 dose of study drug				
Analysis population	Characteristics (mITT)		Lenalidomide 10 mg	Lenalidomide 5 mg	Placebo
		Median age (range), years	68 (36-84)	66 (40 -86)	70 (39 -85)
		Females, %	68	79	80
		Transfusion burden, units/8 week (median, (range))	6 (2 -12)	7 (1 -25)	6 (4 -12)
		IPSS risk category (central review), %			
		Low	49	40	57
		Intermediate	51	60	43
		WPSS risk category, %			
		Very low	0	0	0
		Low	5	15	4
		Intermediate	63	49	65
		High	32	36	29
		Very high	0	0	0
		FAB classification (central review), %			
		RA	68	68	69
		RARS	20	11	16
		RAEB	12	15	6
		CMML	0	4	2
		Other or missing	0	2	8
		EPO level, %			
		≤500 mIU/mL	*34*	28	41
		>500 mIU/mL	*51*	51	47
		Missing	*15*	21	12
		Prior EPO use	*59*	51	47

		Karyotype, %			
		Isolated del(5q)	80	75	75
		Del(5q) ≥1 additional anomaly	20	25	25
		Platelet count, %			
		≥150 x10^9/L	81	77	84
		<150 x10^9/L	20	23	16
		25-50 x10^9/L	2	2	0
	Inclusion	Patients 18 years of age or older with investigator-documented IPSS Low or Intermediate-1-risk MDS with del5q31, with or without additional cytogenetic abnormalities, and RBC transfusion-dependent anaemia (no 8 consecutive weeks without RBC transfusions within the 16 weeks before randomization) were included. Confirmation of del5q31 status (karyotype analysis) and bone marrow morphology was performed by central hematologic review after randomization.			
	Exclusion	Proliferative (white blood cell count ≥ 12 000/µL) chronic myelomonocytic leukaemia; grade≥2 neuropathy; prior use of lenalidomide; use of recombinant erythropoietin (EPO), chemotherapy, or treatment with any other investigational agent within the last 28 days or long-acting erythropoiesis stimulating agents within the last 8 weeks; and abnormal laboratory values (absolute neutrophil count <500/µL, platelet count<25 000/µL, serum creatinine>2.0 mg/dL, serum transaminases>3.0 x upper limit of normal [unless resulting from iron overload from blood transfusions], and serum total bilirubin>1.5 mg/dL)			
Descriptive statistics and estimated variability	Treatment group		*Lenalidomide 10mg*	*Lenalidomide 5 mg*	*Placebo*
	mITT, n		41	47	51
	RBC-TI rates				
		for ≥26 weeks during ≤52 weeks, % (95%CI)	56.1 (39.7 – 71.5) p<0.001[1]	42.6 (28.3 – 57.8) p<0.001[1]	5.9 (1.2 – 16.2)
		for ≥8 weeks using IWG 2000 criteria during ≤52 weeks, % (95%CI)	61.0 (44.5 – 75.8) p<0.001[1]	51.1 (36.1 – 65.9) p<0.001[1]	7.8 (2.2 – 18.9)
		for ≥8 weeks using IWG 2006 criteria during ≤52 weeks, % (95%CI)	61.0 (44.5 – 75.8) p<0.001[1]	51.1 (36.1 – 65.9) p<0.001[1]	5.9 (1.2 – 16.2)
	Duration of erythroid response				
		Protocol defined erythroid response (for ≥26 weeks), median in weeks (95%CI)	NR	NR	NR

[1] Versus placebo

	IWG 2000-defined erythroid response (for ≥8 weeks), median in weeks (95%CI)	NR (82.9 – NR)	NR (41.3 – NR)	-
	CR rates, % Complete Partial Progression	50.0 29.4 20.6 23.5	25.0 15.6 9.4 31.3	0; p<0.001[1] 0 0 14.3
	ITT & safety population, n	69	69	67
	RBC-TI rates for ≥26 weeks during ≤52 weeks, % (95%CI) for ≥8 weeks using IWG 2000 criteria during ≤52 weeks, % (95%CI) for ≥8 weeks using IWG 2006 criteria during ≤52 weeks, % (95%CI)	 55.1 (42.6 – 67.1) p<0.001[1] 60.9 (48.4 – 72.4) p<0.001[1] 60.9 (48.4 – 72.4) p<0.001[1]	 34.8 (23.7 – 47.2) p<0.001[1] 47.8 (35.6 – 60.2) p<0.001[1] 47.8 (35.6 – 60.2) p<0.001[1]	 6.0 (1.7 – 14.6) 7.5 (2.5 – 16.6) 6.0 (1.7– 14.6)
	OS, months median range	 44.5 35.5 – NR	 ≥35.5 24.6 - NR	 42.4 31.9 - NR
	AML Progression at 16 weeks, %	0	2.9	3.0
	FACT-An mean change from baseline at week 12	 5.8 p<0.05[1]	 5.9 p<0.05[1]	 -2.5

Abbreviations: AML = acute myeloid leukaemia, ANC = absolute neutrophil count, CI = confidence interval, CMML = chronic myelomonocytic leukaemia; CR = cytogenetic response, dL = decilitre, EPO = erythropoietin, FAB = French-American-British, FACT-An = functional Assessment of Cancer Therapy-Anaemia, Hgb = haemoglobin, IWG = International Working Group, NR = not reached, mITT= modified intent-to-treat, mg = milligramme, mIU =milli-International Units, µL = microliter, mL = millilitre, OS = overall survival, RA = refractory anaemia, RAEB = RA with excess blasts, RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multi-lineage dysplasia, RBC = red blood cells, WPSS = World Health Organization classification-based Prognostic Scoring System, WHO = World Health Organization

Table 2: Grade 3 or 4 adverse events in ≥5% of patients (double-blind phase)

Grade (according to CTC 3.0)	Outcome, n (%)	Lenalidomide 10mg	Lenalidomide 5mg	Placebo
Grade 3 or 4	Patients with ≥1 AE	65 (94)	62 (90)	29 (43)
	Neutropenia	52 (75)	51 (74)	10 (15)
	Thrombocytopenia	28 (41)	23 (33)	1 (2)
	Leukopenia	6 (9)	9 (13)	0
	Anaemia	2 (3)	4 (6)	6 (9)
	Deep vein thrombosis	4 (6)	1 (1)	1 (2)
Grade 5	Treatment-related death	NA	1 (1%)	NA
Others	AEs requiring dose reduction	38 (55.1)	36 (52.2)	NA
	Dose interruption	32 (46.4)	20 (29.0)	NA

Abbreviations: NA = not available

phase III trial compared lenalidomide 10mg, lenalidomide 5mg and placebo

205 patients overall = intention-to-treat population

This phase III trial compared lenalidomide 5mg and 10mg to placebo. Enrolled patients had to have *investigator* confirmed low/intermediate-1 risk MDS with del(5q31) with or without additional abnormalities and had RBC transfusion dependent anaemia (= 16 weeks prior to randomisation, there were no 8 weeks without RBC transfusions). These 205 patients randomised formed the intention to treat analysis (ITT). Red blood cell transfusion independence (RBC-TI), the primary endpoint was assessed for a modified ITT (mITT) population consisting of 139 patients with *centrally* confirmed low/intermediate-1-risk MDS. Thus, 59%-76% of patients from the initially randomised patients formed the mITT population. The mITT had a median age of 69 years, with the majority (68%-80%) being women. 6 units of RBC transfusions were required within 8 weeks. About 50% of all patients had been previously treated with erythropoetin, and about the same percentage had an erythropoeitin level >500mU/mL. An isolated del(5q31) was the most common cytogenetic abnormality (75%-81%) and platelet counts were within the physiological range in 77%-84%. Concomitant use of G-CSF was allowed.

modified intention-to-treat population:

139 patients with centrally confirmed low/intermediate-1 risk MDS

initially double-blind study, unblinding for patients without minor erythroid response

cross-over was allowed

These 205 patients, the ITT population, were randomised, initially to a double-blind treatment phase. Individuals which showed at least a reduction of 50% in transfusions required (=minor erythroid response) after 16 weeks, stayed in the double-blind phase for up to 52 weeks. Open-label phase therapy was offered for a maximum of 156 weeks to patients without minor erythroid response by week 16, as well as to those which completed the double-blind phase. In addition, patients initially assigned to either the placebo group or the lenalidomide 5mg group without minor erythroid response at 16 weeks were allowed to cross-over to lenalidomide 5mg or 10mg in the open-label phase. Open-label therapy was not offered to patients whose disease progressed and to those with lenalidomide 10mg without minor erythroid response by week 16.

red blood cell transfusion-independence =primary outcome, 56% in 10mg group and 43% in 5mg group in comparison to 6% in placebo group

RBC-TI, the primary endpoint, had to last, as defined by the investigators, for at least 26 weeks and was achieved in 56% in the lenalidomide 10mg group and in 43% of the lenalidomide 5mg group in comparison to 6% in the placebo group of the mITT population. Similar results were found for RBC-TI as defined by the International Working Group criteria 2000 [9] and 2006 (i.e. RBC-TI for ≥8 weeks). Even though subgroup analyses for many characteristic had been performed, comparisons were only made between the two lenalidomide groups and not to placebo. However, besides lenalidomide therapy, higher platelet counts and longer time since diagnosis were identified as predictive factors for RBC-TI. Median duration of erythroid response was not reached yet in any of the lenalidomide groups.

predictive factors were higher platelet counts and longer time from diagnosis

cytogenetic response rates: 50% with 10mg, 25% with 5mg, more than half being complete responses

With a cytogenetic response rate of 50% and in 25% (more than half being complete responses) in the lenalidomide 10mg and 5mg groups, statistical significance was reached in comparison to the placebo group, where no cytogenetic response was observed.

improved QoL results for lenalidomide groups

Health-related QoL was measured using the FACT-An score and showed better outcomes for both lenalidomide groups at 12 weeks and thus prior to cross-over. Short-term AML progression that is at 16 weeks was 3% in the placebo and in the lenalidomide 5mg group and 0% in the lenalidomide 10mg group. Data for median OS are reported but are not meaningful due to cross-over.

1 treatment-related death due to pulmonary embolism

6% of patients had died within 30 days after last dose of placebo or 10mg lendalidomide in contrast to 3% in the 5mg group. The only death thought to be treatment-related was due to pulmonary embolism in the 5mg group. Adverse events (AE) of ≥3 were more frequent in the lenalidomide groups than in the placebo group, with one exception: anaemia was more often observed in the placebo group. At least one AE grade≥3 occurred in 94%, 90% and in 43% in the lenalidomide 10mg, lenalidomide 5mg and in the placebo group respectively. Other AEs more common in the lenalidomide groups were neutropenia, thrombocytopenia and leukopenia, and deep vein thrombosis which was reported in 6% in the lenalidomide 10mg group (2% in the placebo group).

AEs grade ≥3: >90% in lenalidomide groups and in 43% in placebo group

only anaemia more common with placebo therapy

Dose reductions were required in about 50% of patients treated with lenalidomide but no numbers were presented for the placebo arm. The most common reasons for lenalidomide dose reductions were neutropenia (10 mg, 33%; 5 mg, 28%) and thrombocytopenia (10 mg, 22%; 5 mg, 12%).

main reasons for dose reductions and interruptions of lenalidomide: neutropenia and thrombocytopeniam

Dose interruption was reported in 46% and 29% in the lenalidomide 10 mg and 5 mg groups, respectively. The most common reasons for lenalidomide dose interruptions were again neutropenia (10 mg, 23%; 5 mg, 12%) and thrombocytopenia (10 mg 13%; 5 mg 12%).

6.2 Efficacy and safety - further studies

phase II which formed based for FDA approval enrolled 148 patients

A phase II study (MDS-003) enrolled 148 patients with low/intermediate-1 risk MDS and del5q31 either alone or in addition to other cytogenetic abnormalities [21]. The vast majority of patients had an isolated del5q (74%), but some patients had also 5q syndrome (27%), del(5q) plus 1 additional abnormality (17%) or had even complex (≥3) abnormalities (8%) [29]. This

study, published in 2006, served as basis for the FDA's decision for market licensing in the U.S.

RBC-TI in 67%

Enrolled patients had transfusion-dependent anaemia and were treated with 10mg lenalidomide which was initially given for 21 consecutive days in a 28 day cycle (in 46 patients), but dosing was changed to daily administration later on (in overall 102 patients). Previous therapeutic regimens included erythropoietin (73%), chemotherapy (39%) and iron-chelation therapy (37%). RBC-TI, the primary outcome, was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatment period was achieved in both dosing schedules in 99 patients (=67%), showing no relevant difference between the two groups. An additional 13 patients (=9%) required at least 50% fewer transfusions. Response to lenalidomide therapy occurred rapidly (median 4.6 weeks). Haemoglobin levels rose in patients with TI by 5.4 g/dl and median peak haemoglobin concentration in these patients was 13.4 g/dl. 53 patients (=53% of TI individuals) remained transfusion independent for at least 1 year at a median follow-up of 104 weeks. Rates of TI were investigated according to specific clinical as well as pathological features, showing only a significant difference for platelet counts and transfusion need prior to therapy. If platelet counts were ≥100,000/μl 73% of individuals treated achieved TI in contrast to 39% of patients with <100,000/μl. Similarly, better outcomes were seen for patients who required <4 units/8 weeks RCT. Of 85 evaluable patients, 45% had a complete cytogenetic response which was defined as the absence of cells in metaphase containing any abnormal clone at 24 weeks; 28% had a partial response. This outcome was independent of karyotype complexity. Estimated median OS was 7.6 years for patients with del(5q) only and 5.6 years for patients with more than one abnormality at a median follow-up of 3.8 years. Progression to AML occurred in 8 out of 106 patients.

rapid response, haemoglobin levels increased by 5.4 g/dl

rates of TI were influenced only by platelet counts and transfusion need

3 patients (2%) died due to treatment

dose adjustments in 84%, interruptions in 20%

In terms of AEs, neutropenia (grade ≥3: 55%) and thrombocytopenia (grade ≥3: 44%) were the most common ones and occurred within the first eight weeks of therapy. 11 patients died, of which 3, that is 2%, believed as treatment-related were attributed to neutropenic infection. Dose adjustments were necessary in 84% and 20% stopped lenalidomide therapy due to AEs.

long-term follow up data after 3 years from 42 patients

continuous TI in 29% and transient TI in also 29%

36% progressed to AML

responders had significant reduced risk of AML progression

Göhring et al. present long-term follow-up data from all European patients enrolled at the MDS-003 study [22]. At a median follow-up of 3.3 years, overall 42 patients were included of which 6 were assigned after the closure of the MDS-003 trial. 29% achieved a continuous TI and the same percentage achieved a transient TI. Initially 48%, that is 20 patients, had a cytogenetic response but it remains unclear if these were complete or partial responses. During follow-up, 12 of these patients lost cytogenetic responses. At a median time of 51 months, 36% had progressed to AML of which all but one patient died. The authors also analysed relationship of several factors such as age, gender or IPSS risk score to AML progression and found differences for patients with or without erythroid/cytogenetic responses. Patients with erythroid/cytogenetic responses had a significantly decreased risk of AML progression at three (10%) and five years (21%) than non-responders at three years: 46%, at five years: 60%. During progression to AML, most of the clones with del(5q) acquired additional chromosome aberrations and developed into complex clones. Thus, genetic instability and clonal evolution seem to be the driving forces of leukaemic transformation in MDS patients treated with lenalidomide. Even though patients with responses progressed more rarely to AML than those without responses, the small sample size limited significance of these findings.

compassionate use programme: TI in 65%

platelet count was again predictive factor

AEs similar to previous studies

matched control group: OS similar in both groups

A compassionate use programme, conducted in France, comprised 95 patients with low risk MDS with del(5q) [23]. Of these, the majority had isolated del(5q) (79%) whereas the rest had 1 (14%) or more than 1 additional (6%) abnormality. Treatment consisted of 10mg lenalidomide daily for 21 days every 28 days for at least 16 weeks. TI was achieved in 65% of patients and platelet count at baseline or a platelet decrease by ≥50% was again the only factors associated with prediction of TI. During follow-up (median 18 months) 6 patients (6%) progressed to AML. Higher grade AEs were similar to those reported in the previous studies, since the most common ones were thrombocytopenia (40%) and neutropenia (74%), side effects which caused three deaths. 10% developed venous thromboembolism and dose reductions or treatment discontinuation due to AEs were reported for 48%. Another publication compared these patients to a historical control group of 99 patients with lower risk MDS with del(5q) who were never treated with lenalidomide [27]. After controlling for potential confounders (due to the non-randomised control), 71 matched patients were found in both groups. For these, the estimated cumulative incidence of AML from diagnosis was 9% in the lenalidomide group and 16% in the control group, yielding no significant difference. Also, OS was similar in the two groups (p=0.06).

open-label study with 11 patients, but only 5 were transfusion dependent but became TI

An open-label study enrolled 11 Japanese patients with low risk MDS with a del(5q) abnormality [24]. 5 had transfusion dependent anaemia and 6 were TI but had symptomatic anaemia. Treatment consisted of 10mg lenalidomide in a 28 day cycle. All 5 patients achieved TI and haemoglobin levels rose from 7.1 to 12.7g/dL, but improvements in haemoglobin levels were also found for patients with TI. Grade ≥3 AEs were neutropenia (91%), leukopenia (55%), lymphopenia (27%) and thrombocytopenia (9%). A total of 8 (73%) patients had lenalidomide dosages reduced from 10 mg daily to 5 mg daily (21 consecutive days). Furthermore, administration was temporarily interrupted in 8 (73%) patients due to AEs. The reason for the dose reduction as well as for dose interruption was grade ≥3 neutropenia.

post-marketing surveillance data from 7,700 patients to assess venous thromboembolism

increased risk for embolism when lenalidomide was administered concurrently with erythropoietic stimulating agents

venous thromboembolism rate: <1%

Yang et al. [25] investigated occurrence of venous thromboembolism (i.e. deep vein thrombosis and pulmonary embolism) in 7,764 MDS patients with lenalidomide exposure between December 2005 and December 2007 which had been identified by the RevAssist®, the restrictive distribution programme in the U.S. Information on cases of venous thromboembolism was obtained from the company's post-marketing surveillance safety database. For calculation of disproportional signal scores, a technique which allow assessment of associations between drug exposure and occurrence of side-effects but not of causal relationships, a commercial version of FDA' Adverse Event Reporting System database was used. Since risk group and cytogenetic abnormalities were not routinely collected, these characteristics could not be specified. To test if concurrent administration of ESAs increased the risk of venous thromboembolism, three different categories were formed: patients with lenalidomide but without ESA, patients with ESA in the absence of lenalidomide and patients exposed to both lenalidomide and ESA. Only if lenalidomide and ESAs were administered concurrently, a statistically association was found, but not if lenalidomide only was used. Reported rates of venous thromboembolism were 0.53%.

Goss et al. [26] conducted a cost-effectiveness analysis of lenalidomide (10mg) and best supportive care without erythropoietin in comparison to best supportive care (BSC) with erythropoietin. This study, which was sponsored by the manufacturer, calculated the costs for an American setting based on the rate and duration of TI as assessed in the MDS-003 trial [21] in comparison to patients from the "Nordic MDS Group" trials and the placebo controlled arm of a phase III-MDS trial. When costs of medications, transfusions, chelation, laboratory test, office visits and other resources were calculated for the outcomes measures TI and quality-adjusted life-years, lenalidomide yielded an incremental 0.53 transfusion-free and 0.25 QALYs compared to BSC at 1 year. Total treatment costs, also at 1 year, were $ 63,400 for lenalidomide and $ 54,900 for BSC. These numbers results in an incremental cost-effectiveness ratio of $ 16,000 per transfusion-free year and in $ 35,000 per QALY gained and were thus considered as cost-effective for the American setting.

cost-effectiveness analysis in the US

sponsored by manufacturer

based on phase II study results cost-effectiveness within American threshold

7 Estimated costs

In Austria, the costs for one package 10mg lenalidomide containing 21 tablets for the labelled indication are € 5,475 [30]. Without any required dose reductions or interruptions this would be the costs for one 28 days cycle.

€ 5,500 for a 28-days cycle

Savings might incur due to fewer transfusions required and hence a less frequent use of hospital services. Moreover, transfusion dependent patients with del(5q) treated with supportive care alone will shortly accumulate iron overload and should receive due to their potentially benign clinical course iron chelation treatment. Older MDS patients are mostly not candidates for intravenous infusions of iron chelation therapy and receive therefore oral therapy at considerable costs. Achieving TI thus prevents accumulation of iron overload and saves the cost of iron chelation therapy. On the other hand, additional therapy with G-CSF factors might be indicated and hospital admissions for the treatment of AEs might increase.

8 On-going research

On www.clinicaltrials.gov 3 on-going phase III studies for the investigated indication were found:

3 on-going phase III trials

NCT01243476: a phase III multi-centre, randomized, double blind, placebo controlled trial and with two arms designed to assess the efficiency and toxicity of the scheme lenalidomide versus observation in a series of 60 patients with low risk MDS associated to 5q deletion with anaemia (Hb≤12g/dL) but without the need of transfusion. Estimated study completion date is January 2016.

NCT00843882: a randomized phase III trial studying lenalidomide to see how well it works with or without epoetin α in treating patients with MDS

and anaemia, sponsored by the National Cancer Institute. The estimated Study Completion Date was September 2009, yet no results are available.

NCT01029262: The purpose of this study is to investigate whether lenalidomide would reduce the number of RBC transfusions needed by anaemic (RBC transfusion-dependent) subjects with low or intermediate-1 risk MDS without a deletion 5q chromosome abnormality. The study will also investigate the safety of lenalidomide use in these subjects. Two-thirds of the subjects will receive lenalidomide and one-third of the subjects will receive placebo (does not contain lenalidomide). Estimated study completion date is December 2017.

On www.clinicaltrialsregister.eu no phase III trial was found for MDS.

9 Commentary

FDA: licensed based on phase II study

EMA: not licensed due to concerns of comparative data for AML progression

but already "off-label" use in Austria

In the U.S., lenalidomide was licensed in 2005 for patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) abnormality with or without additional cytogenetic abnormalities [24]. The MDS-003 trial [31], a single-arm phase II study, formed the basis for the FDA's decision. Even though the FDA's Oncologic Drugs Advisory Committee expressed concerns that a single-arm trial does not allow proper assessment of lenalidomide's safety profile, a favourable benefit-risk profile was confirmed [32]. The EMA, on the other hand, has not granted market authorisation for this indication, because of lack of comparative data for the risk of AML progression [16, 33]. However, the drug is already used in Austria [34].

FDA safety announcement in May 2012: increased risk of developing new types of cancer

In May 2012, the FDA released a safety announcement, notifying the public that patients with newly diagnosed multiple myeloma which had been treated with lenalidomide had almost a three-fold increased risk of developing new types of cancer, especially AML, MDS and B-cell lymphoma malignancies [35]. A pooled analysis of three RCTs showed second primary malignancies in 7.9% in the lenalidomide group in comparison to 2.8% ($p<0.001$) in the groups which had not received lenalidomide. Healthcare professionals are thus advised to weigh this risk against the potential benefits of the drug when considering initiation of Revlimid® therapy. In Europe, EMA's Committee for Medicinal Products for Human Use concluded that efficacy gains such as an improved overall survival justify the associated risks despite a four-fold increase in the number of new cancers (solid tumours and cancers of the blood and the immune system) in patients treated with lenalidomide for multiple myeloma, which is the licensed indication in Europe [36].

Therapy of low/intermediate-1 risk MDS aims at improving cytopenia associated symptoms. The treatment of anaemia, the most frequent cytopenia, increases quality-of-life and extends survival by reducing risk of heart-failure [37]. Lenalidomide was investigated in patients with low/intermediate-1-risk MDS and with del(5q), but it remains unclear which additional features, besides del(5q), patients have to show. Some authors suggest that lenalidomide can be used in patients with thrombocytopenia/neutropenia [3], whereas others point out that patients with a low platelet/neutrophil count were excluded from both the phase III study and the phase II study [8]. Moreover, erythropoietin treatment failure [19, 37] or serum erythropoietin level >500 mU/mL [3] are discussed as prerequisites for treatment initiation. In contrast, some evidence suggests that response to erythropoetin is lower in patients with del(5q) MDS than in other, low-risk MDS [38]. Also, further gene mutations might determine prognosis and thus choice of therapy [8] as, for example, evidence suggests that non-responders to lenalidomide may have an increased risk of developing chromosomal abnormalities and have consequently a higher risk of AML progression [22]. Therefore, patients should be monitored for cytogenetic response by using both fluorescence in situ hybridization and karyotyping to determine if and when treatment should be initiated and stopped [39].

unclear if lenalidomide is also indicated for patients with low platelet/neutrophil count

erythropoietin levels also relevant?

other gene mutations..?

The two studies, mentioned above, included to a great extent similar patients which are representative for the target population [20, 31]: more women were enrolled, median age was about 70 years and the majority of patients did not have thrombocytopenia; more than 75% of patients had an isolated del(5q). More patients had received prior erythropoetin therapy (73%) in the study by *List et al.* [31] than in the RCT (52%) [20] but the median number of RBC transfusions in the 8 weeks before the studies' start was 6 in both trials. RBC-TI for ≥26 weeks was achieved in 56% of patients treated with lenalidomide 10mg in comparison to 6% in the placebo group. In the uncontrolled trial TI for ≥56 days was observed in 67% overall. Complete and partial response rates for the 10mg group was 29% and 21% and 0% for the placebo group. The phase II study showed a complete response in 45% and a partial response in 28%. Due to cross-over at 16 weeks, longer-term results for AML progression from the phase III are difficult to interpret. Only 11 patients (out of 67) had never received lenalidomide. Of these 4 (i.e. 36%) progressed. Of patients allocated to the lenalidomide 10mg group, 22% progressed to AML. In the phase II study, corresponding numbers were 8%.

transfusion independence in >50%

complete/partial responses in 29%/21% in lenalidomide 10mg group

cross-over compromised long-term outcomes of phase III trial

In terms of AEs, myelosuppression occurring early in the treatment course was the most frequent one. In the placebo-controlled trial, grade ≥3 thrombocytopenia and neutropenia was observed in 41% and 75% in the 10mg group and in 2% and 15% in the placebo group during the double-blind treatment phase. Any AE grade ≥3 was seen in 94% of patients treated with 10mg in contrast to 43% of patients treated with placebo. In the lenalidomide groups, dose reductions were necessary in about 50% and treatment interruption was reported in 46% (10mg group) and 29% (5mg group) [20]. Rates of deep vein thrombosis were 6% [20] and 3% in the two groups [31]. A subgroup analysis of the phase II study population conducted by the sponsor and confirmed by the FDA, revealed that AEs occurred twice as often in patients aged over 65 years [32]. No such information is provided for the phase III study but would be of high interest, since MDS patients are usually diagnosed with 70 years.

myelosuppression most common AE

dose reductions in 50%

deep vein thrombosis: 6%

AEs more common in individuals >65 years

lenalidomide alternative besides transfusions and growth factors

Therapeutic options for patients with low/intermediate-1 risk MDS are transfusion of RBC and erythropoietic growth factors ± G-CSF [37]; for patients with del(5q) lenalidomide offers an alternative. Despite improved (short-term) outcomes for patients treated with lenalidomide in comparison to placebo, the impact on OS remains unclear. However, RBC-TI clearly offers advantages for patients because time consuming hospital visits for repeated RBC transfusions are replaced by an oral drug [38]. This also implies that, at least in Austria, costs would be shifted from hospitals to the social health insurance. Nonetheless, potential savings due to a reduced number of hospital admissions for RBC transfusion and reduced need of costly iron chelation therapies might be outweighed by admissions for the treatment of AEs and by the rather expensive drug itself. However, estimating overall costs for lenalidomide is difficult, since the optimal treatment duration as well as the dosage remain unclear, because evidence indicates that interruption of lenalidomide therapy 6 months after complete cytogenetic remission rather than continuation until disease progression may achieve prolonged TI, a fact which would reduce costs [4].

unclear impact on OS

but fewer hospital visits due to reduced transfusion need

oral administration also advantage

some evidence suggests that risk of AML progression not increased by lenalidomide

Another question concerns occurrence of secondary malignancies and progression to AML. The latter one was assessed in the phase III study, but median time to progression was not reached in the lenalidomide groups and results are compromised due to cross-over. Some evidence from registries and retrospective analyses, published more or less by the same group of authors, indicates that the risk of AML progression and occurrence of second primary malignancies are not increased by lenalidomide therapy [27, 40, 41]. The same authors also retrospectively compared outcomes of patients <65 years to patients ≥65 years whom had been included in the phase III study and in the MDS-004 trial (published as abstract only) [42]. Even though they found similar rates of RBC-TI ≥ 26 weeks, younger patients achieved cytogenetic remissions less often and more patients progressed to AML. However, long-term outcomes from direct comparisons between lenalidomide treated and untreated patients are needed to ultimately judge these risks.

but long-term outcomes from direct comparisons are needed

BUT: impact on development of secondary malignancies unclear?

It seems as patients can benefit from lenalidomide at the expenses of severe AEs and potential secondary cancers. Thus further refinement of criteria for patient selection (e.g. number of chromosomal abnormalities or transfusion need at diagnosis), close observation with dose reductions/interruptions if necessary and follow-up investigations to identify non-responders are basic prerequisites to avoid exposure to lenalidomide therapy and potential secondary tumours of patients which do not benefit from this therapy.

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