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Transfusion independence and cytogenetic response in myelodysplastic syndromes. What this means for the patient

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Myelodysplastic syndromes (MDS) constitute a spectrum of haematopoietic stem cell malignancies characterized by ineffective haematopoiesis, peripheral cytopenia, and increased risk of acute myeloid leukaemia (AML). Refractory anaemia is the presenting feature in approximately two-thirds of patients, with anaemia usually developing in the remainder as the disease progresses. Transfusion dependence is associated with impaired quality of life and increased mortality, making strategies to restore effective erythropoiesis a critical therapeutic challenge.^{1,2} About 40% of the *International Prognostic Scoring System* (IPSS) lower-risk patients are transfusion-dependent, and this dependency increases up to 80% in higher-risk patients.³

Currently, allogeneic stem cell transplantation offers the only potentially curative treatment, but is generally reserved for those patients with higher-risk disease in whom age and other comorbidities are not limiting. While supportive therapy with erythropoietin and granulocyte colony-stimulating factor (G-CSF) yields erythroid responses in up to 20-30% of selected patients, the innovative use of select immunomodulatory drugs potentially offers the greatest potential to achieve long-term transfusion independence for select karyotypes. Lenalidomide is one of a select group of proprietary drugs having immunomodulatory properties, an IMiDs[®] compound that is unique among emerging drug therapies in that it yields cytogenetic remissions and durable erythroid responses in MDS patients with chromosome 5q deletion.

Clinical impact of transfusion dependence

Current management of anaemia in patients with MDS relies on red blood cell transfusions to alleviate symptoms,

or attempts to improve red blood cell production through the administration of erythropoietin and G-CSF. However, dependence on blood transfusions predisposes over time to secondary haemochromatosis, increased risk of viral infection, and adversely impacts survival and quality of life.^{2,4} In a study performed by investigators at the University of Pavia, Italy, 467 patients with *de novo* MDS were retrospectively evaluated for clinical and haematological features at diagnosis, progression to leukaemia, and overall survival.² The investigators found that transfusion dependence and the degree of transfusion burden negatively affected overall and leukaemia-free survival in patients with lower-risk disease (Table 1). The *World Health Organization* (WHO) classification of MDS had prognostic relevance, with significant differences in survival reported between patients with refractory anaemia (RA), refractory cytopenia with multilineage dysplasia, and RA with excess blasts (RAEB) types 1 and 2. Transfusion-dependent patients with lower-risk (<5% marrow blasts) WHO phenotypes had a significantly reduced survival compared to patients who did not require transfusions at frequencies of every 3 months or less ($p < 0.001$). This effect did not reach statistical significance in patients with excess blasts due to the shorter overall survival. Overall survival in patients without excess blasts declined incrementally with each additional unit of blood transfused over a 4-week period and for every 500 ng/mL rise in serum ferritin above a 1000-ng/mL threshold, providing strong support for the impact of transfusion burden and secondary iron overload on survival in these patients. Surprisingly, the transfusion load-related effect on survival was associated with an incremental increase in the risk of progression to AML, implying that anaemia severity

Table 1. Negative impact of transfusion dependence on overall survival (OS) and leukaemia-free survival (LFS) in patients with myelodysplastic syndromes. (Data from Malcovati L, *et al.*²)

	OS		LFS	
	Hazard ratio	p value	Hazard ratio	p value
Transfusion dependence vs transfusion independence	2.16	<0.001	2.02	<0.001
Transfusion dependence as predictor of poor outcome, accounting for cytogenetic risk (good, intermediate, poor)	1.72	0.007	2.64	<0.001
Transfusion burden, defined as total number of RBC units transfused (<20, 20–40, >40)	1.21	0.02	1.39	<0.001
Transfusion burden, defined as number of units transfused monthly	1.35	<0.001	1.75	<0.001

Abbreviation: RBC, red blood cells.

reflects the magnitude of MDS clone's maturation impairment. However, patient mortality related not only to leukaemia-associated deaths, but also to excess cardiac and other events related to iron overload.² Besides decreasing survival and increasing progression to AML, transfusion dependence in MDS contributes to impaired quality of life.¹ In particular, symptoms of fatigue and dyspnoea were increased compared with the age- and sex-adjusted reference population.

Current strategies for managing transfusion-dependent anaemia

Treatment with recombinant erythropoietin, either alone or with the addition of G-CSF, has assumed a central role in primary treatment for anaemia in MDS. In a long-term follow-up analysis of 123 evaluable MDS patients enrolled in 3 Nordic MDS Group studies investigating erythroid response to treatment with erythropoietin and G-CSF, the combination produced an erythroid response in 39% of patients, with a median response duration of 2 years.⁵ The majority of patients enrolled in these studies had Low-/Int-1-risk MDS, defined according to IPSS criteria, and these patients achieved a significantly higher response rate compared with a smaller population of patients with Int-2-/High-risk MDS. All patients were analysed according to erythropoietin response probability profile, which applies 2 variables: (1) transfusion burden (≥ 2 units/month); and (2) serum erythropoietin concentration >500 U/L, the combination of which portends a low probability of response. Only 1 of 16

patients (6%) in the poor-response group responded to treatment compared with 8 of 44 patients (18%) in the intermediate group, and 25 of 42 patients (60%) in the good-response group. Patients with Int-2- or High-risk MDS also showed a lower response to treatment than did patients with Int-1- or Low-risk MDS.

As expected, survival was longer in patients with lower-risk disease compared with higher-risk disease.⁵ Although erythropoietin response variables of serum erythropoietin level and transfusion burden have not previously been associated with survival, the survival was longer in patients with the favourable response profile than for those in the intermediate and poor response profile groups. Thus, patients who are least likely to have a favourable response to cytokine therapy are those with either more advanced disease, or those patients with high endogenous serum erythropoietin level and transfusion dependence and greater severity of maturation impairment. The use of the *French-American-British* (FAB) classification system in this study prevented a more thorough investigation of risk; however, the WHO system has recently been shown to offer additional discrimination for response to erythropoietin and G-CSF.⁶ The presence of multilineage dysplasia lowers the probability of response, owing to a striking difference in response rate between refractory anaemia with ringed sideroblasts (RARS) and refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD/RS) (75% versus 9%; $p=0.003$). Moreover, patients with single-lineage erythroid dysplasia and less than 5% marrow

blasts had better survival rates than those with multilineage dysplasia and less than 5% marrow blasts.

In addition to erythropoietic improvement and prolongation of survival, improvement in quality of life in MDS patients with expectation for extended survival is an important priority. The relationship between haematologic improvement and quality of life was demonstrated in a study that included 53 MDS patients with transfusion-dependent anaemia. Quality of life improved coincident with anaemia response to treatment with erythropoietin and G-CSF, with a significantly better quality-of-life score associated with a complete (haemoglobin >115 g/L without need for red blood cell [RBC] transfusion) or partial (increase in haemoglobin of 15 g/L or more for patients with non-transfused anaemia or a 100% reduction in transfusions) erythroid response to treatment compared with non-responders using the Nordic MDS Group criteria.¹ The importance of obtaining a complete or major erythroid response was further supported by a significantly longer duration of response in complete responders compared with those who achieved a partial response. Thus, erythroid response to treatment may improve quality of life in MDS patients, including patients with transfusion dependence.⁷

These findings indicate that active therapies are needed to improve the rate and quality of erythroid response, which thereby may impact quality of life and possibly survival. Current supportive treatment strategies including erythropoietin and G-CSF are effective in a relatively small proportion of patients.

Lenalidomide in the management of transfusion-dependent MDS

To date, the agent that has shown the most promise in restoring erythropoiesis and reducing transfusion dependence in MDS is the IMiDs® compound lenalidomide (CC-5013; Revlimid®). Lenalidomide has a number of pharmacologic effects that include suppression of vascular endothelial growth factor (VEGF)-induced angiogenic response, stimulation of innate and acquired immune mechanisms including the activation of natural killer cells and T-cells, and suppression of tumour necrosis factor alpha and other inflammatory-molecule production by monocytes.⁸ Lenalidomide also has the ability to directly suppress the growth and promote apoptosis in some tumour cells, which in combination with its modulatory effects on the endothelium

and immune system have made it a potent anti-tumour drug. In combination with erythropoietin, lenalidomide augments signal transducer and activator of transcription 5 (STAT5)-mediated signal transduction through the erythropoietin receptor, overcoming the suppression in MDS of erythropoietin-induced STAT5 activation in erythroid precursors.⁹

The efficacy and safety of lenalidomide in patients with MDS and either transfusion-dependent or symptomatic anaemia have recently been explored in an open-label, dose-finding phase I/II study (MDS-001).¹⁰ Eligible patients had a histologically confirmed diagnosis of primary MDS according to FAB criteria for at least 3 months prior to enrolment, and either symptomatic anaemia defined as a haemoglobin level less than 10 g/dL or transfusion-dependent anaemia defined by the need for at least 4 units of RBCs within 8 weeks of enrolment. Patients had either failed to respond to erythropoietin treatment or had an endogenous serum erythropoietin level greater than 500 U/L and heavy transfusion burden (≥2 units/month). Patients with severe neutropenia or thrombocytopenia, treatment-related MDS, or clinically significant comorbidity were excluded. A total of 43 patients were enrolled and received oral lenalidomide at a dose of 25 mg/day, 10 mg/day, or 10 mg/day for 21 days of every 28-day cycle. Final response was assessed after 16 weeks of therapy, with responders continuing treatment until disease progression, treatment failure, or dose-limiting toxicity. Patients with haematological improvement that did not qualify as a protocol-defined response were eligible to continue treatment for a further 8-week period, before a final response assessment at 24 weeks. The primary study endpoint was erythroid response defined according to International Working Group criteria that had to be maintained for at least 8 weeks; a major erythroid response was defined as transfusion independence or an increase in haemoglobin level of more than 2 g/dL; a minor erythroid response was defined as a 50% or greater reduction in transfusion dependence or a sustained elevation in haemoglobin level of 1-2 g/dL.

The 43 enrolled patients had a median age of 72 years (range 28-85), a male (58%) predominance, and a median disease duration of 29 months (range 3-169). In total, 33 patients (77%) had either RA or RARS, and 38 (88%) had Low or Int-1 IPSS risk scores. Thirty-two patients (74%) were transfusion-dependent and 33 (77%) had previously failed to respond to erythropoietin treatment, while 13 patients (30%)

Table 2. Erythroid responses in patients with myelodysplastic syndromes with transfusion-dependent anaemia or symptomatic anaemia treated with lenalidomide in an open-label phase I/II study. (Adapted from List A, *et al.*¹⁰)

Lenalidomide dose (mg/day)	n	Erythroid response, n (%)			Time to response (weeks)	
		Major	Minor	Total	Median	Range
25	13	6	0	6 (46)	9.0	2.5-18.5
10	13	6	1	7 (54)	10.5	2-17.5
10 (for 21 days)	17	9	2	11 (65)	11.5	6-24
Total	43	21 (49)	3 (7)	24 (56)	–	–

had failed to respond to thalidomide. Moderate-to-severe neutropenia and thrombocytopenia were present in 28% and 23% of patients, respectively, and 37% of patients had at least 2 cytopenias. Twenty patients (47%) had clonal karyotypic abnormalities, including 12 patients with interstitial deletions of chromosome 5q31 (del 5q) either isolated (n=11) or with an additional cytogenetic abnormality. Of the 43 patients enrolled, 24 achieved an erythroid response in an intention-to-treat analysis for an overall response rate of 56%, including 21 patients who achieved a major response (Table 2). Patients with a major response reached a median response haemoglobin of 13.2 g/dL (range 11.5-15.8), which corresponded to a median increase in haemoglobin from baseline of 5.3 g/dL (range 4.4-8.7). Seven patients who achieved a major response have an ongoing response for longer than 4 years and remain transfusion-independent, including 4 patients with del 5q. The mean haemoglobin level maintained in these patients has been 12.6 g/dL (range 10.3-14.3).

Of the 36 cytogenetically informative patients, 20 had an abnormal karyotype at baseline. Of these 20 patients, 11 had a 50% or greater reduction in the number of abnormal metaphase cells, and 10 achieved complete cytogenetic remission by week 16, including 9 patients with del 5q. All cytogenetic responses occurred in patients who also had a haematological response. The median time to response was more rapid in patients with del 5q (8.0 weeks; range 2.5-16) than in patients with other karyotype abnormalities or a normal karyotype (11.2 weeks; range 2-26). These findings suggested that erythroid response to lenalidomide was karyotype-dependent.

Treatment-associated myelosuppression was common, with 28 of 43 patients (65%) experiencing grade 3-4 neutropenia, and 23 patients (53%) experiencing grade 3-4 thrombocytopenia. The frequency of treatment-related neu-

tropenia was dose-dependent, with grade 3-4 neutropenia occurring in 77% of patients treated with lenalidomide 25 mg/day compared with 62% of patients treated with 10 mg/day, and 47% of patients treated with 10 mg for 21 days over a 28-day cycle. The median interval between the first interruption of treatment and resumption was 22 days (range 9-55) in each dosage cohort.

Two phase II multicentre studies (MDS-002, MDS-003) were performed to confirm the karyotype-dependent erythropoietic activity of lenalidomide in MDS.¹¹⁻¹³ The 2 studies were of similar design, recruiting patients with Low/Int-1 IPSS transfusion-dependent MDS with either del 5q (MDS-003) or other cytogenetic abnormalities (MDS-002). Eligible patients had transfusion-dependent anaemia requiring more than 2 units of RBCs every 8 weeks and a 16-week pre-study documentation of transfusions, absolute neutrophil count above 500/ μ L, and platelets above 50,000/ μ L. Lenalidomide was administered orally at either 10 mg/day for 21 days every 28 days or at 10 mg/day, with response assessed after 24 weeks of treatment. The primary endpoint of each trial was transfusion independence after 24 weeks of therapy, with transfusion independence defined as freedom from transfusion for at least 8 weeks and an increase in haemoglobin of at least 1 g/dL.

Among 148 patients in the del 5q MDS-003 trial, median age was 71 years (range 37-95), 66% were female, and median duration of disease was 2.5 years (range 0.1-20.7).¹³ Median RBC burden was 6 units every 8 weeks, and 105 patients (71%) required at least 2 units of RBCs every 4 weeks. Overall, 73% of patients had previously been treated with recombinant erythropoietin; and 74% of patients had isolated del 5q, but just 27% met the criteria for the 5q syndrome. Another 17% of patients had del 5q with an additional cytogenetic abnormality, and 8% had del 5q with a complex karyotype.

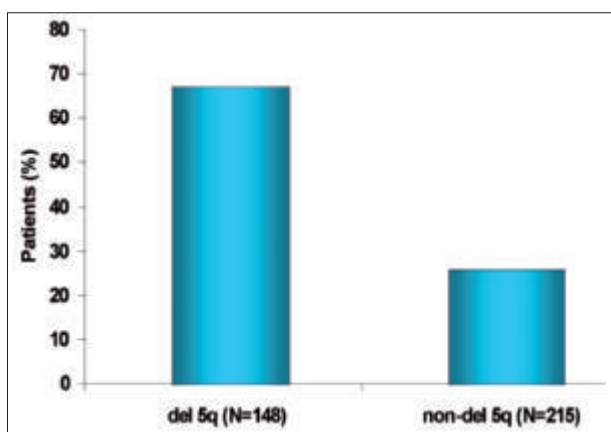


Figure 1. Proportion of patients achieving transfusion independence following treatment with lenalidomide in trials MDS-003 (del 5q) and MDS-002 (non-del 5q). (Data from List AF, *et al.*¹²)

In an intention-to-treat analysis, 99 of 148 patients (67%) achieved transfusion independence by week 24 (Figure 1), independent of dosage schedule.¹¹⁻¹³ Another 9% of patients had a 50% or greater reduction in transfusions by week 24 for a transfusion response rate of 76%. Median time to response was 4.6 weeks (range 1.0-4.9), indicating a rapid rise in haemoglobin level, with a median increase from baseline of 5.4 g/dL to a maximum response haemoglobin of 13.4 g/dL. With a median follow-up of 104 weeks, the median duration of transfusion independence has yet to be reached, but is greater than 74 weeks, indicating that the response to lenalidomide in patients with del 5q is durable.^{12,13}

When response was assessed according to cytogenetic pattern, there was no difference in the proportion of erythroid responders in patients with either isolated del 5q or those with del 5q and 1 other abnormality, or those with 3 or more cytogenetic abnormalities (72%, 48%, and 67%, respectively).¹³ The overall cytogenetic response rate among evaluable patients was 73%,* including 45% of patients with a complete cytogenetic response. In patients with isolated del 5q, 77% achieved a cytogenetic response, which again was similar to patients with del 5q and 1 other abnormality (67%) or del 5q and >1 other abnormalities (50%). A complete histological response was observed in 38 of 106 evaluable patients (36%), including 14 of 19 patients with RAEB and 9 of 14 patients with RARS, while 8 patients had progression to a more advanced MDS type and 8 progressed to AML after 2 years median follow-up. Moderate to severe neutropenia (55%) and thrombocytopenia (44%) were the most common adverse events necessitating treatment inter-

ruption or dosage adjustment which generally occurred early in the treatment course.^{11,13}

The MDS-002 trial involved 215 patients with a non-del 5q karyotype, the median age was 72 years (range 27-94), 64% were male, and 86% required at least 2 units of RBCs every 4 weeks.^{11,12} In a preliminary, intention-to-treat analysis performed on data available by 15 March, 2005, 56 of 215 patients (26%) achieved transfusion independence (Figure).¹² In this population, 77% had a normal karyotype, with no differences observed in transfusion independence between patients with a normal karyotype versus an abnormal karyotype. As of the March 2005 analysis, the median duration of response exceeded 40 weeks.

Lenalidomide-induced transfusion independence was associated with a median haemoglobin increase of 3.0 g/dL in responding patients.¹² Neutropenia and thrombocytopenia were, once again, the most common adverse events, but recorded in fewer than 25% of patients.

Ongoing clinical trials of lenalidomide in MDS

Several studies of lenalidomide in MDS are either ongoing or are soon to be under way. A phase I/II study of lenalidomide in combination with erythropoietin is currently being completed, while a phase III placebo-controlled trial (MDS-004) is further investigating the efficacy and safety of lenalidomide in patients with del 5q in which patients are randomized to 5- or 10-mg doses of lenalidomide, or placebo, with assessment of response after 24 weeks. Lenalidomide is also being investigated in a phase III trial to evaluate its efficacy alone and in combination with darbepoetin alfa in the treatment of Low-/Int-1-risk MDS.

Conclusions

Transfusion dependence negatively impacts survival and quality of life in patients with lower-risk MDS. While the impact is greatest among patients with a high transfusion burden, even patients with low transfusion dependence may benefit from achieving complete transfusion independence. Erythropoietic cytokines alone often fail to produce improvements in transfusion burden. In contrast, a substantial propor-

*Note: the data provided here have been updated since the symposium and are based on final data, now published in *N Engl J Med* 2006; 355:1456-65.

tion of patients with Low-/Int-1-risk MDS have achieved a significant reduction in transfusion requirement as a result of treatment with lenalidomide. Lenalidomide is particularly effective in patients with del 5q with or without other karyotypic abnormalities. Ongoing trials will continue to explore the use of lenalidomide in MDS among patients with different disease and cytogenetic profiles, and in combination with other agents. The side-effect profile of lenalidomide is manageable and consistent with the mechanism of action. Lenalidomide is the first drug to receive Food and Drug Administration regulatory approval for the treatment of transfusion-dependent anaemia due to Low- or Int-1-risk MDS associated with del 5q with or without other cytogenetic abnormalities. With the capacity to restore normal cytogenetics in many patients, lenalidomide may potentially alter the natural history of disease, even in those patients with greater karyotype complexity.

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