Immunomodulating Drugs in Myelodysplastic Syndromes

Lionel Adès¹ and Pierre Fenaux¹

¹Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France

Based on immune mechanisms that appear to play an important role in the pathophysiology of at least part of the lower-risk myelodysplastic syndrome (MDS), the immunomodulating drug (IMID) thalidomide and its derivative lenalidomide (LEN) have been used in MDS, principally in lower-risk MDS. LEN has become the first-line US Food and Drug Administration (FDA)–approved treatment for lower-risk MDS with 5q deletion (del5q), in which its main mechanism of action is probably a direct cytotoxic activity on the del5q clone. This possibly specific effect is currently being investigated in higher-risk MDS—and even acute myeloid leukemia (AML)—with del5q, but LEN has also demonstrated some efficacy in MDS and AML without del5q. Thalidomide also has some activity in lower-risk MDS without del5q, but its side effects limit its practical use in these patients.

Introduction

Immune mechanisms appear to play a role in the pathophysiology of at least some of the lower-risk (including International Prognostic Scoring System low and intermediate 1) myelodysplastic syndrome (MDS). Immune suppression with antithymocyte globulin (with or without cyclosporine) or, more recently, with alemtuzumab, has been used successfully in some of these patients¹,² (this treatment will not be covered in the present review). Also based on those immune mechanisms, the immunomodulating drug (IMID) thalidomide and its derivative lenalidomide (LEN) have been used in MDS, principally in lower-risk MDS. Due to its probably direct cytotoxic activity on the del5q clone in lower-risk MDS with this cytogenetic abnormality, LEN is also currently being investigated in higher-risk MDS (and even AML) with del5q. Thalidomide also has some activity in lower-risk MDS without del5q, but its side effects limit its practical use in that context. Finally, another IMID, pomalidomide, is demonstrating clear efficacy in myeloma and myelofibrosis,³,⁴ but has not so far been extensively tested in MDS.

Thalidomide in MDS

Thalidomide has shown some efficacy in the treatment of anemia in lower-risk MDS, with erythroid responses observed in approximately 35% of patients who could receive the drug for at least 8–12 weeks.⁵-⁹ However, in a published series, 20%-50% of the patients discontinued the drug rapidly, mainly due to side effects including fatigue, sleepiness, or constipation. Increasing the daily dose to > 200 mg did not appear to increase the response rate, but did increase the side effects. Conversely, lowering the daily dose to 100 or even 50 mg was associated with fewer side effects, but somewhat lower response rates.⁵ Responders generally required drug discontinuation after several months due to persistence of the same side effects or to the occurrence of peripheral neuropathy. Side effects of thalidomide may be more important in MDS than in myeloma, possibly due to the somewhat older median age of MDS patients compared with myeloma patients.⁵

In the published literature, response to thalidomide is almost exclusively seen on the erythroid lineage and is mainly observed in patients with no excess of marrow blasts. The mechanism of action of thalidomide in MDS is not clearly known. Thalidomide suppresses the synthesis of TNF-α by activated monocytes, partly inhibits angiogenesis by inhibiting β-fibroblast growth factor, and has been shown to costimulate T cells and exert complex immunomodulating activities.¹⁰,¹¹ In our experience, pretreatment VEGF levels were lower in responders compared with nonresponders, whereas microvessel density and apoptosis decreased in responders but were unchanged in nonresponders.³

Relatively little is known on the efficacy of thalidomide in patients with del5q. In a series of 24 patients, we observed an erythroid response thalidomide in 1/3 of the patients, but responses were generally short, and there was no difference between MDS with and without del5q.¹² We also found in the literature 31 cases of MDS with del5q treated with thalidomide, and 5 (16%) of them had an erythroid response.⁶,⁸,⁹,¹³ In those patients and in our series, cytogenetic response (CyR) was evaluated in responders. Strupp et al reported a complete and a partial CyR to thalidomide in 2 MDS patients with del5q who had achieved erythroid response to thalidomide.¹³ Overall, however, the effect of thalidomide in MDS with del5q appears similar to that seen in MDS without del5q, a major difference with LEN.

Thalidomide has also been tested in combination with other drugs in MDS, including azacitidine in higher-risk MDS¹⁴ and arsenic trioxide¹⁵ or erythropoietin (EPO)¹⁶ in lower-risk MDS, but the number of patients was too small to draw any conclusions. Combination with EPO, however, seemed to be associated with an increased risk of deep venous thrombosis.

LEN in lower-risk MDS with del5q

Efficacy of LEN in lower-risk MDS with del5q and prognostic factors of response

LEN has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1–risk MDS with del5q, with or without additional cytogenetic abnormalities, based on phase 2 studies showing the dramatic effect of LEN in these patients.¹⁷,¹⁸ This effect was particularly useful because lower-risk MDS patients with del5q tend to have a relatively poor response to erythropoiesis-stimulating agents (ESAs).¹⁲

The first large trial evaluating LEN was the MDS 003 trial, which evaluated a dose of 10 mg/d as a continuous treatment or 3 weeks...
Deep venous thrombosis (DVT) and/or pulmonary embolism were reported in 0.53% of >7500 MDS patients treated with LEN in a post-marketing experience in the United States, although the incidence was higher in patients with concurrent use of EPO.25 However, DVT was observed in 8 of the 95 patients treated in the French ATU program, although only one of them had a previous history of DVT26; 6 of those patients were responders, and there was a trend for more DVT in patients with a rapid increase in hemoglobin. Prophylactic measures of DVT in MDS treated with LEN are not codified, except in patients with a history of DVT, in whom preventive anticoagulation appears justified.23

Rash is frequent with LEN in MDS, but is generally transient, whereas diarrhea can be long-lasting, with limited efficacy of the usual drugs.17,18

**Mechanisms of action of LEN in lower-risk MDS with del5q**

Several mechanisms of action are believed to contribute to the therapeutic effect of LEN, including: (1) an effect of LEN on the immune system, with cytokine production, T- and natural killer-costimulation, and a disputed role on natural killer T cells26,27; (2) stimulation of erythropoiesis, with significant increases in the proportion of BM erythroid precursor cells and in the frequency of clonogenic progenitor cells; (3) substantial improvement in the adhesion profile of BM CD34+ cells; and (4) anti-inflammatory effects and angiogenesis inhibition.

The main mechanism of action of LEN appears to be a direct antiproliferative activity in cells with del5q. LEN was indeed shown to induce a G0/G1 cell cycle in a cell line with del5q,29 as well as a specific suppression of cell growth by apoptosis, through the inhibition of cytokinesis.30 In patient cells, selective growth inhibition of MDS del5q progenitors not affecting the growth of normal cells was seen.31 The best defined molecular mechanism of this clonal suppression appears to be the inhibition of the nuclear sequestration of the haploinsufficient cell-cycle regulatory proteins cdc25c and PP2A alpha by LEN, which promotes selective G2 arrest and apoptosis. Suppression by shRNA of Cdc25C and PP2Aalpha gene expression recapitulated del5q susceptibility to LEN with induction of G2 arrest and apoptosis in non del5q MDS cells.32 However, other mechanisms may play a role, as shown in particular by a case report in which LEN led to RBC transfusion independence in a child whose del5q was very small, not encompassing Cdc25C and PP2Aalpha.33 Up-regulation by LEN of the tumor-suppressor gene SPARC could be one of these other mechanisms.31

The finding of a direct inhibitory effect of LEN on the del5q clone is compatible with the higher incidence and magnitude of cytopenias observed after LEN onset in MDS patients with del5q compared with MDS without del5q and the complete CyRs observed.17

RBC-TI can be achieved in the absence of CyR. Furthermore, a recent study provided in vivo evidence of the persistence of stem cells with del5q in patients treated with LEN who became transfusion independent; the stem cells were selectively resistant to LEN therapy.34 Those findings suggest that complete eradication of the malignant stem-cell population is not mandatory to obtain a clinical response, and may explain the high frequency of disease recurrence...
Does LEN increase the risk of AML evolution in lower-risk MDS with del5q?

Whereas LEN is FDA approved for lower-risk MDS with del5q, the European Medicines Agency raised concern over the potential risk of LEN to trigger AML progression in some lower-risk MDS with del5q, and did not approve this drug for MDS, asking for additional analyses. No prospective randomized trial comparing the long-term outcome of lower-risk MDS with del5q treated with and without LEN has been performed. Such a trial may now be difficult to conduct given the dramatic effect of LEN on anemia in this MDS subset and its approval for this indication in many countries.

Several studies recently reevaluated the rate of progression to AML in lower-risk MDS with del5q treated before the LEN era or with LEN. The Dusseldorf group reported a 2- and 5-year AML progression rate of 7% and 18%, respectively, in 300 lower-risk MDS patients with del5q treated without LEN. However, the rate was higher, approximately 30%, in RBC-transfusion-dependent patients, who represent precisely the patients included in LEN trials. This AML progression rate was similar to that observed in the MDS 003 trial when patients had received LEN. In addition, in the MDS 003 trial, a notable proportion of the patients who progressed to AML already had signs of progression upon inclusion in the trial. In the MDS 004 trial, the cumulative 3-year AML-progression rate was 34.8%. Achievement of RBC-TI with LEN was associated with a significantly reduced risk of AML progression (by ~45%), which does not support possible triggering of AML progression by the drug. Finally, using the propensity score method, the Groupe Francophone des Mye’lodysplasies (GFM) recently reported the incidence of progression to AML in a cohort treated with LEN to be no greater than that of a comparable historical cohort of lower-risk MDS with del5q treated without LEN. Likewise, no significant survival difference was found between the 2 groups.

Perspectives with LEN in other types of MDS (and in AML)

LEN in higher-risk MDS (and AML) with del5q

LEN as a single agent. As described above, the main mechanism of action of LEN seems to be a direct inhibitory effect on del5q clones, and this can be exploited in higher-risk MDS (or even AML) with del5q.

The GFM conducted a phase 2 trial of LEN (10 mg/d) in high- and intermediate-2-risk MDS with del5q, including 18 patients with 20%-30% marrow blasts (World Health Organization–defined AML). The karyotype was complex in most patients, with several abnormalities in addition to del5q; 47 patients were included. Response (including CRs, PRs, and BM CRs) was achieved in 28% of the patients. Treatment was associated with significant myelosuppression requiring hospitalization in most cases. Absence of cytogenetic abnormalities in addition to del5q and baseline platelets > 100 000/mm³ were significant predictors of CR by univariate and multivariate analyses, both in the whole patient population and when the analysis was restricted to World Health Organization–defined MDS. In particular, 6 of the 9 patients with isolated del5q reached CR, versus none of the patients with additional cytogenetic abnormalities. In another experience in elderly AML patients with del5q, most of whom had BM blasts > 30% and complex karyo-

type, LEN at daily doses up to 50 mg/d showed overall modest activity with 14% PRs or CRs.

Those findings supported the concept of a direct inhibitory activity of LEN on the del5q clone, which was only effective when LEN was used as a single agent in cases of isolated del5q. This prompted the design of treatments combining LEN and other drugs in these patients.

LEN in combination with other drugs. Little is known about the combination of LEN with chemotherapy. Anthracycline-AraC combinations give low CR rates (approximately 20%) in higher-risk MDS or AML with del5q (generally as part of complex karyotypes). The GFM recently conducted a phase 2 study combining LEN and escalating doses of anthracycline-AraC–intensive chemotherapy in higher-risk MDS and AML patients with del5q. In this cohort of elderly patients with very poor cytogenetics, the CR rate was 50%, higher than that generally reported with chemotherapy alone in similar patients. Disease-free survival, however, remained short (9 months), suggesting that induction or consolidation therapy should be improved. We also recently started a phase 2 study combining LEN and azacitidine in higher-risk MDS patients with del5q considered unfit for the intensive chemotherapy–LEN trial based on the relatively limited efficacy of azacitidine alone in patients with complex karyotypes including del5q and the feasibility of this combination in terms of safety, as assessed by Sekeres et al.

LEN in MDS without del5q

LEN as a single agent. In a large phase 2 study in lower-risk MDS with anemia resistant to ESAs (or with poor prognostic factors of response to ESAs such as both a high RBC transfusion requirement and high baseline EPO level), LEN yielded RBC-TI in 27% of the patients, with an additional 17% experiencing a significant reduction in RBC-TD. The median response duration in this study was 41 weeks. Favorable karyotype and limited RBC-TD were associated with better responses. A molecular signature predicting LEN response was identified, consisting of a cohesive set of erythroid-specific genes with decreased expression in responders, suggesting that a defect in erythroid differentiation underlies the LEN response. Consistent with this observation, treatment with LEN promoted erythroid differentiation of primary hematopoietic progenitor cells grown in vitro.

Patients with refractory anemia with ringed sideroblasts associated with marked thrombocytosis may be especially sensitive to LEN, as suggested by a very preliminary report of 2 patients who became transfusion independent, 1 of them achieving a complete molecular remission based on JAK2 mutation assessment.

LEN in combination with other drugs. The combination of LEN and azacitidine was studied in MDS without del5q in a phase 1 study in 18 patients with higher-risk MDS. In this escalating dose study, the maximum tolerated dose was not reached. The overall response rate was 67%, including 44% CR, 17% hematologic improvement, and 6% BM CRs; this response rate was higher than that generally reported with azacitidine as a single agent, once again suggesting a role for LEN in MDS/AML without del5q.

LEN in AML. As seen above, LEN appears to have a certain selectivity of action in myeloid clones harboring del5q, explaining some of the effect in higher-risk MDS but also in AML with del5q. Conversely, in a phase 2 study in untreated AML with intermediate- or poor-risk cytogenetics without del5q, LEN induced significant
responses when used at a high dose (50 mg/d). Of the 33 patients enrolled, 30% achieved CR, with a median CR duration of 5 months. In those patients without del5q, hematological toxicities were relatively moderate, including grade III-IV thrombocytopenia in 67%, anemia in 55%, and neutropenia in 33% of the patients. The mechanism whereby LEN induces CR in AML without del5q remains unknown, and this warrants additional studies. Mesa et al reported the presence of trisomy 13 as a possible prognostic factor of response to LEN in AML without del5q, but in small patient numbers, also requiring confirmation by additional studies.

Conclusion
Whereas LEN is the first-line treatment for lower-risk MDS with del5q, it may also prove to be effective in higher-risk MDS (and AML) with del5q, based on its apparent direct suppressive effect on del5q clones. However, LEN also appears to be effective in MDS and AML without del5q through other mechanisms of action.

Disclosures
Conflict-of-interest disclosure: L.A. has received research funding from Celgene. P.F. has received research funding and honoraria from Celgene. Off-label drug use: LEN in lower-risk MDS without del5q clones. However, LEN also appears to be effective in MDS and AML without del5q through other mechanisms of action.

Correspondence
Pierre Fenaux, MD, PhD, Service d’hématologie clinique, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris 13 University, France; Phone: 33(1)48 95 70 50; Fax: 33(1)48 95 70 58; e-mail: pierre.fenaux@avc.aphp.fr.

References


