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Introduction

MELETIOS DIMOPOULOS

Department of Clinical Therapeutics
University of Athens School of Medicine
Athens, Greece

Certain immunomodulatory drugs are establishing a role in the treatment of several haematological malignancies, including myelodysplastic syndromes (MDS), multiple myeloma (MM), and chronic lymphocytic leukaemia (CLL). The use of these drugs, together with recent advances in our understanding of the underlying molecular pathways that affect the course of disease, is changing the way we approach the management of patients with haematological malignancies. To address these recent developments, a satellite symposium was held as part of the 11th Congress of the European Hematology Association in Amsterdam, The Netherlands, in June 2006. The purpose of the symposium was to reflect on how the development of a select proprietary group of drugs having immunomodulatory properties, the IMiDs® compounds, is affecting the way we treat certain haematological malignancies, and to review clinical data on lenalidomide, an IMiDs® compound that appears to have applications in a wide variety of haematological malignancies.

Lenalidomide mechanism of action

The anticancer effects of lenalidomide observed in the clinic are thought to be related to its ability to affect multiple cell processes that are directly or indirectly involved in cancer cell growth and survival. In MM cells, for example, lenalidomide has been shown to directly inhibit growth and promote apoptosis (Figure 1).[1,2] It also inhibits the adhesion of MM cells to stromal cells in the bone marrow. In stromal cells, lenalidomide reduces the expression of pro-angiogenic factors, such as vascular endothelial growth factor and basic fibroblast growth factor. Stromal cell expression of other factors that promote MM cell growth, such as interleukin-6 and tumour necrosis factor alpha (TNF-α), is also inhibited by lenalidomide. In addition, lenalidomide stimulates immune cells, such as T-cells and natural killer cells. The multiple effects of lenalidomide that target cancer cells directly or indirectly by modifying the microenvironment represent a novel treatment approach that is translating into clinical efficacy in a variety of haematological malignancies.

Development of select IMiDs® compounds

Lenalidomide and certain other IMiDs® compounds are structurally related to thalidomide, which became commercially available as a sedative in 1956, but was withdrawn from most markets in 1961 due to evidence of its teratogenic effects.[1,3,4] Later, thalidomide was shown to be an effective treatment for erythema nodosum leprosum, an acute inflammatory state that occurs in patients with leprosy.[5] The effects of thalidomide in this setting were later attributed to its ability to inhibit TNF-α production in human blood monocytes.[6] In 1998, the US Food and Drug Administration approved its use for patients with erythema nodosum leprosum associated with leprosy, provided that it was distributed through a restricted-access programme (System for Thalidomide Education and Prescribing Safety – *S.T.E.P.S*) to prevent foetal exposure. Based on its ability to inhibit TNF-α, thalidomide continued to be evaluated in a number of non-malignant indications, such as rheumatoid arthritis, Crohn's disease, and HIV. Further research on the biological effects of thalidomide revealed anti-angiogenic and immunomodulatory effects.[7,8] This led to the investigation of thalidomide as an anticancer drug, and initial results in patients with refractory MM

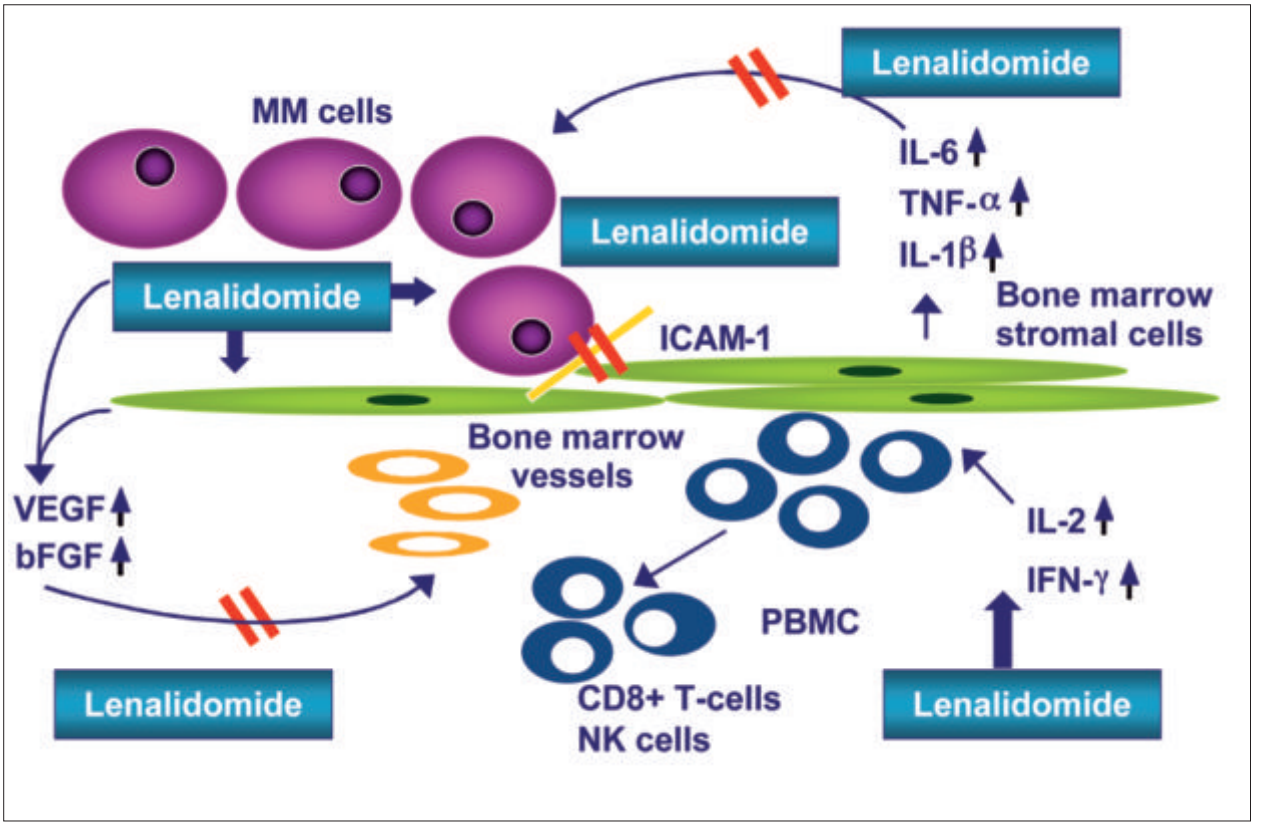

Figure 1. Anti-tumour activity of select immunomodulatory drugs in multiple myeloma: lenalidomide targets MM cells in the bone marrow microenvironment. (Adapted with permission from Richardson PG, *et al.*[2])
Abbreviations: bFGF, basic fibroblast growth factor; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-gamma; IL, interleukin; MM, multiple myeloma; NK, natural killer; PBMC, peripheral blood mononuclear cell; TNF-α, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

were promising, although the exact mechanism responsible for the anticancer effects of thalidomide was unclear.[9] Thalidomide has also been used successfully as a component of first-line therapy for newly diagnosed MM and continues to be evaluated in the treatment of a variety of solid tumours and haematological malignancies.[10]

Development of lenalidomide and other IMiDs® compounds began in the 1990s.[1] These compounds were created to improve the efficacy and reduce the side effects associated with thalidomide. Lenalidomide is a more potent inhibitor of TNF-α and stimulator of T-cells, compared with thalidomide.[11] Notably, lenalidomide did not produce teratogenic effects in the sensitive New Zealand rabbit model – the only model in which thalidomide-related teratogenicity has been detected.[1] These findings led to the clinical evaluation of lenalidomide in the treatment of several haematological malignancies, including MDS, MM, and CLL.

Lenalidomide in MDS

In his article, Alan List reviews clinical evidence of the efficacy and safety of lenalidomide in patients with MDS. Recent studies show that treatment with lenalidomide reduces the transfusion requirement in patients with Low- or Int-1-risk MDS, and leads to transfusion independence in a substantial proportion of patients.[12–14] This effect was seen in patients with and without del 5q, although it was more pronounced in those with del 5q. The primary adverse events were neutropenia and thrombocytopenia, which were manageable, but required weekly monitoring during the first 8 weeks of treatment. Given that transfusion dependence is associated with poor quality of life, higher risk of leukaemic transformation, and reduced survival in patients with MDS, achieving transfusion independence could have a meaningful impact on clinical outcomes, even in patients with low-risk, transfusion-dependent MDS.[15] Ongoing trials are continuing

to evaluate the use of lenalidomide in the treatment of MDS.

The fact that lenalidomide is particularly effective in patients with del 5q highlights the importance of cytogenetic evaluation in patients with MDS. Aristoteles Giagounidis reviews our current understanding of how cytogenetic features, particularly del 5q, influence prognosis. With the incorporation of the 5q- syndrome in the recently developed World Health Organization classification system, cytogenetic analysis has become an essential part of the management of all patients with MDS.[16] Further research is needed to clarify how the presence of various cytogenetic abnormalities or combinations of abnormalities can influence clinical outcomes, such as leukaemic transformation and survival. The observation that lenalidomide is particularly effective in patients with del 5q is the first example of how cytogenetic features of MDS can be used to determine appropriate treatment options.

Lenalidomide in MM

In his review of the clinical evidence supporting the use of lenalidomide in patients with relapsed/refractory MM, Pieter Sonneveld highlights the strikingly similar results reported from 2 large multicentre phase III trials comparing the combination of lenalidomide plus dexamethasone with dexamethasone alone.[17,18] Both trials found that the addition of lenalidomide prolonged time to progression. The incidence of adverse events was also similar in both trials; the primary side effect attributed to lenalidomide was neutropenia. Notably, the incidence of adverse events typically associated with thalidomide, such as severe peripheral neuropathy, sedation, and constipation, were rarely reported with lenalidomide. Recent analyses of these studies found that the efficacy of lenalidomide was not affected by prior treatment with thalidomide or the number of prior treatments in heavily pretreated patients.[19,20] Investigation of lenalidomide in various settings for the treatment of MM continues.

Lenalidomide in CLL

The growth and survival of CLL cells depends on cytokine signalling from the microenvironment, and lenalidomide downregulates various cytokines that could affect CLL cell growth and survival.[21] Asher Chanan-Khan reports on the Roswell Park Cancer Institute experience with lenalidomide in CLL. In their phase II study in patients with relapsed/refractory disease, the overall response to lenalidomide was 41%, including a complete response rate of 7%.[22] As in other clinical studies of lenalidomide, the primary treatment-related adverse event was neutropenia, which required dose reduction in some patients. Tumour flare reactions were also observed, characterized by increased swelling of the lymph nodes, low-grade fever, and rash. Prophylactic use of low-dose prednisone may reduce the incidence, severity, and duration of flare reactions.[23] Based on these preliminary results, it appears that lenalidomide is active in patients with relapsed/refractory CLL, and may represent a novel approach to the treatment of CLL, by targeting the tumour microenvironment. Additional studies of lenalidomide in CLL are planned, including a phase III trial comparing the efficacy and safety of 2 dosing regimens of lenalidomide patients with relapsed/refractory disease.

Conclusions

Selected IMiDs® compounds such as lenalidomide represent a novel approach to the treatment of haematological malignancies. The multiple effects of lenalidomide on cancer cells and the microenvironment are translating into clinical efficacy across a diverse spectrum of haematological malignancies. The experience with lenalidomide provides a good example of how our understanding of the clinical, biomolecular, and genetic features of haematological malignancies is being used to improve patient outcomes. With the advent of lenalidomide, it is clear that the way we treat MDS, MM, and other types of cancer is changing rapidly.

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