S-LX, J-LL and J-YZ contributed equally to this paper.

[1]Department of Hematology; [2]Jiangsu Institute of Hematology, the First Affiliated Hospital of Soochow University, Suzhou, China; [3]Department of Radiotherapy and Oncology; and [4] School of Nursing of Soochow University, Suzhou, China.

Correspondence: De-Pei Wu and Sheng-Li Xue, Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, 215006, P. R. China.

E-mail: wudepei@suda.edu.cn/slxue@suda.edu.cn

Key words: severe congenital neutropenia, HAX1, compound heterozygous mutation, chronic myelomonocytic leukemia.

Funding: this work was supported by a grant from the government of Jiangsu Province (A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, PAPD2011).

Acknowledgments: the authors are indebted to the patient and his family for participating in this study and would like to thank Y Chen and L-J Cao for their assistance.

Citation: Xue S-L, Li J-L, Zou J-Y, Su J, Chen S-N, and Wu D-P. A novel compound heterozygous HAX1 mutation in a Chinese patient with severe congenital neutropenia and chronic myelomonocytic leukemia transformation but without neurodevelopmental abnormalities. Haematologica 2012; 97(2):318-320. doi:10.3324/haematol.2011.055038

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Carlsson G, Andersson M, Pütsep K, Garwicz D, Nordenskjöld M, Henter JI, et al. Kostmann syndrome or infantile genetic agranulocytosis, part one: celebrating 50 years of clinical and basic research on severe congenital neutropenia. Acta Paediatr. 2006;95(12):1526-32.
2. Klein C. Molecular basis of congenital neutropenia. Haematologica. 2009;94(10):1333-6.
3. Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schäffer AA, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet. 2007;39(1):86-92.
4. Carlsson G, Elinder G, Malmgren H, Trebinska A, Grzybowska E, Dahl N, et al. Compound heterozygous HAX1 mutations in a Swedish patient with severe congenital neutropenia and no neurodevelopmental abnormalities. Pediatr Blood Cancer. 2009; 53(6):1143-6.
5. Lanciotti M, Indaco S, Bonanomi S, Coliva T, Mastrodicasa E, Caridi G, et al. Novel HAX1 gene mutations associated to neurodevelopment abnormalities in two Italian patients with severe congenital neutropenia. Haematologica. 2010;95(1):168-9.
6. Ishikawa N, Okada S, Miki M, Shirao K, Kihara H, Tsumura M, et al. Neurodevelopmental abnormalities associated with severe congenital neutropenia due to the R86X mutation in the HAX1 gene. J Med Genet. 2008;45(12):802-7.
7. Germeshausen M, Grudzien M, Zeidler C, Abdollahpour H, Yetgin S, Rezaei N, et al. Novel HAX1 mutations in patients with severe congenital neutropenia reveal isoform-dependent genotype-phenotype associations. Blood. 2008;111(10):4954-7.
8. Carlsson G, van't Hooft I, Melin M, Entesarian M, Laurencikas E, Nennesmo I, et al. Central nervous system involvement in severe congenital neutropenia: neurological and neuropsychological abnormalities associated with specific HAX1 mutations. J Intern Med. 2008;264(4):388-400.
9. Chao JR, Parganas E, Boyd K, Hong CY, Opferman JT, Ihle JN. Hax1-mediated processing of HtrA2 by Parl allows survival of lymphocytes and neurons. Nature. 2008;452(7183):98-102.
10. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, ed. WHO Classification of tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon 2008.
11. Matsubara K, Imai K, Okada S, Miki M, Ishikawa N, Tsumura M, et al. Severe developmental delay and epilepsy in a Japanese patient with severe congenital neutropenia due to HAX1 deficiency. Haematologica. 2007;92(12):e123-5.
12. Zeidler C, Donadieu J, Bolyard AA, Vandenberghe P, Pracht G, Beaupain B, et al. Update On the Risk of Leukemia in Genetic Subgroups of Congenital Neutropenia (CN): Comparison of Patients with Known Gene Mutations (ELA2, HAX1, WASP, G6PC3, p14). Blood (ASH Annual Meeting Abstracts). 2009; 114:3597.

POEMS syndrome with severe neurological damage clinically recovered with lenalidomide

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal component, and skin changes) is a paraneoplastic disorder associated with an underlying plasma cell dyscrasia. Associated features to this syndrome are sclerotic bone lesions, elevated levels of vascular endothelial growth factor (VEGF), Castleman's disease, endocrinopathies, papilledema, peripheral edema, effusions, ascites, thrombocytosis and fatigue.[1] The pathogenesis of the POEMS syndrome is not well understood, but it is likely that proangiogenic[2] (such as VEGF) and proinflammatory cytokines[3] (such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1 and interleukin (IL)-6) play an important role in the pathogenesis of this disease.

Therapy for POEMS syndrome has not been standardized. So far, many different strategies have been used, including radiotherapy, chelating agents and corticoids, immunoglobulins, plasmapheresis, and high doses of chemotherapy followed by peripheral blood stem cell transplant (SCT).[4] Monoclonal antibodies, like rituximab (anti-CD20) or bevacizumab (anti-VEGF), have also been used. Recently, immunomodulatory drugs (IMiDs), such as thalidomide or lenalidomide, have emerged as therapeutic options in these patients because they are powerful drugs against malignant plasma cells which reduce the production of proinflammatory and proangiogenic cytokines. Both drugs have shown efficacy in improving the clinical condition of patients with POEMS syndrome.[5-7] Lenalidomide has the additional advantage of being associated with a much lower risk of peripheral neuropathy than thalidomide. Similarly, concerns about exacerbating neuropathy also arise when other new therapeutic agents, such as bortezomib, are taken into consideration.

We present the clinical outcome of 10 patients with POEMS syndrome who were treated at different centers in Spain with lenalidomide as salvage therapy from 2007 to 2010. This restrospective study was approved by the MD Anderson Cancer Center Madrid Scientific Committee (Institutional Review Board). Age at entry ranged from 39 to 63 years and patients' condition fulfilled published diagnostic criteria.[1] Main clinical features of POEMS syndrome are described in Table 1. All patients had motor-sensory polyneuropathy, predominantly affecting the lower limbs, monoclonal plasmaproliferative disorder and sclerotic bone lesions. Of note, neurological symptoms led to a restrictive ventilatory alteration in 2 cases (ns. 4 and 5), and confined patients to a wheelchair or to bed in 7 cases (ns. 3, 4, 5, 6, 7, 8 and 10).

All patients had received previous treatments to lenalidomide therapy (Table 2), including 4 cases who had received chemotherapy (melphalan-containing regimens, cyclophosphamide or polychemotherapy treatment), one who was treated with rituximab, and 6 who had received immunoglobulin treatment. Local radiation therapy was administered in 2 patients for sclerotic

Table 1. Patients' clinical characteristics.

Patient	Age/Sex	PN	MPD	SBL	CD	Org	Edema	Endocrinopathy	Skin changes	Papiledema	Others
1	63 / M	+	+	+	+	-	-	-	-	-	-
2	39 / M	+	+	+	-	-	-	+	+	-	-
3	47 / M	+	+	+	-	-	+	+	+	-	Polycythemia
4	49 / M	+	+	+	-	+	-	+	+	-	RVD
5	63 / F	+	+	+	-	-	-	-	-	-	RVD
6	54 / M	+	+	+	+	-	+	+	+	-	Thrombocytosis Polycythemia, RVD
7	54 / M	+	+	+	-	-	+	-	-	-	Thrombocytosis
8	65/ M	+	+	+	-	-	+	+	+	-	-
9	53 / F	+	+	+	-	+	-	+	+	+	Thrombocytosis
10	59/ F	+	+	+	-	+	+	+	+	-	Thrombocytosis

PN: polyneuropathy; MPD: monoclonal plasmaproliferative disorder; SBL: sclerotic bone lesions; CD: Castleman's disease; Org: organomegaly; RVD: restrictive ventilatory disease.

Table 2. Treatment and response.

Patient	Age/sex	Diagnosis	Previous treatments	Starting date lenalidomide	Cycles number	Neurological	Response M protein	Other	AutoSCT
1	63 / M	Jul/05	Rituximab/Igs/Pred	Feb/08	Len/Dex 8	Improvement	Ifx neg		-
2	39 / M	May/08	Pred/Igs	Jul/08	Len/Dex8	Improvement	Ifx pos		-
3	47 / M	Nov/08	MP	Mar/09	Len/Dex6	Improvement	Ifx neg	Resolution of edema	Jan/10
4	49 / M	Jan/07	Cy/RT	Feb/08	Len/Dex 12	Resolution	Ifx neg	Resolution of diaphragmatic paralysis	-
5	63 / F	Feb/06	MP/RT/ VBMCP/VBAD	Feb/09	Len/Dex 6	Resolution	Ifx neg	Resolution of ventilatory alteration	-
6	54 / M	Mar/08	Igs/Prednisone	Mar/08	Len/Dex 18	Improvement	Ifx pos	Improvement in respiratory insufficiency	July/09
7	54 / M	Mar/07	MP	May/07	Len/Dex 6	Resolution	Ifx pos		Jan/08
8	65/ M	Jun/07	Igs/Prednisone	Sep/07	Len/RT 13	Resolution	Ifx neg		April/08
9	53 / F	Jul/09	Igs	Aug/09	Len/Dex 6	Improvement	Ifx pos	Improvement in edema, hepatomegaly and thrombocytosis	March/10
10	59 / F	Apr/10	Igs	May/10	Len/dex 7	Improvement	Ifx pos		-

Igs: intravenous immunoglobulins; Pred: prednisone; Ifx: immunofixation; MP: melphalan/prednisone; Cy: cyclophosphamide; RT: radiation therapy VBMCP/VBAD, vincristine, carmustine, nelphalan, cyclophosphamide, prednisone, adriamicyn, dexamethasone.

lesions. Median follow up of 4 (range 1-36) months showed minimal or no clinical improvements in response to these therapies.

All but 3 patients received salvage treatment with combined therapy of lenalidomide 25mg/day for 21 days in 28-day cycles with dexamethasone (40 mg/week). Two patients (case ns. 3 and 10) received the prior scheme with a lower dose of lenalidomide (15 mg/day) and another patient was treated with lenalidomide alone at 25 mg/day (case n. 8). Median number of lenalidomide courses was 7.5 (range 6-18): 4 patients received 6 cycles, 2 patients received 8 cycles, and 4 patients received 7, 12, 13 and 18 cycles, respectively. All patients showed clinical improvement after lenalidomide treatment, even those who later underwent an SCT (Table 2). Due to the delayed responses observed with treatments like melphalan, some effect of the previous treatment could have contributed to the responses observed (case ns. 3, 4 and 5). Clinical resolution of neuropathy was observed in 4 cases and in the remaining patients a significant improvement in neurological symptoms was reported. None of the patients confined to a wheelchair needed further administration of the study treatment and all but 3 regained a fully independent walk; these 3 patients needed support with crutches or assistance. With respect to the M-component, a negative immunofixation was reached in 5 patients.

Treatment tolerance was optimal and only 2 patients (case ns. 1 and 9) developed episodes of respiratory infections that led to a transient discontinuation of therapy; therapy was restarted (with lower doses in case n. 1) after clinical resolution. In all cases for whom PBSC harvest was programmed (n=5), a sufficient number of $CD34^+$ cells was collected. No particular toxicity was observed after the PBSC autologous transplantation performed in 5 patients; melphalan 200mg/m^2 was used as conditioning regimen in 4 cases and 100 mg/m^2 in one other case. Transplant could have contributed clinically to the favorable outcome of the patients.

Our data indicate that lenalidomide is an effective treatment for POEMS syndrome. In fact, several POEMS syndrome cases treated with lenalidomide have demon-

strated favorable responses.[5-11] Dispenzieri and co-workers were the first to suggest the efficacy of the lenalidomide and dexamethasone combination for POEMS syndrome after its administration led to a marked improvement in one patient. This improvement was particularly evident at a neurological level with recovery of the ability to walk; improvements in functional status, VEGF and IL-6 levels, skin changes and anasarca were also observed.[5] Similarly, another patient was able to walk further and climb stairs without assistance after 4 cycles of this therapy.[9] Also, an unusual case of POEMS syndrome with Kappa restriction showed improved symptoms and the resolution of the associated neuropathy[6] after lenalidomide treatment.

These data agree with the favorable outcomes shown in the 10 patients described here. These patients experienced systemic improvement, especially of the polyneuropathic condition, after receiving lenalidomide. All patients achieved improved extremity mobility and strength, and patients confined to a wheelchair or bedbound (n=7) regained the ability to walk. This is one of the most relevant advances in terms of the quality of life of the patients, since one of the main characteristics of this syndrome is the fact that peripheral nerves are compromised. In addition, other improvements included the disappearance of or a decrease in monoclonal component, at the level of bone capture, edema and achromatosis, as well as a reduction in organomegalia.

The favorable responses shown in the 10 cases presented show the efficacy of lenalidomide in recovery from the neurological damage associated with POEMS syndrome, both at sensory and motorary levels. Neurological damage is, in fact, one of the more devastating manifestations of the progression of this disease. Therefore, these observations support the use of the immunomodulatory agent lenalidomimde in patients with POEMS syndrome. The treatment-related adverse events associated with lenalidomide, reported for 2 of the patients, were largely predictable and manageable.

José F. Tomás,[1] Pilar Giraldo,[2] Ramón Lecumberri,[3] and Sara Nistal[4]

[1]Department of Hematology, MD Anderson Cancer Center, Madrid; [2]Hematology Service, Hospital Miguel Servet, Zaragoza; [3]Hematology Service. University Clinic of Navarra, Pamplona, and [4]Hematology Service, Hospital Infanta Leonor, Madrid, Spain.

Correspondence: José F. Tomás MD, PhD, Department of Hematology, MD Anderson Cancer Center Madrid, Arturo Soria 270. 28033 Madrid, Spain. Adjunct Professor, Department of Lymphoma and Myeloma, The University of Texas, USA. E-mail address: jftomas@mdanderson.es

Key words: POEMS syndrome, lenalidomide, neurological, recovery.

Acnowledgments: the authors appreciate the contribution of Dr G. Ramirez,[1] Dr A. Mendizabal[2] and Dr J. Prieto[3] who contributed with one case to the series. ([1]Hospital Virgen de la Victoria, Malaga, [2]Hospital Txagorritxu, Vitoria and [3]Hospital San Pedro de Alcántara. Cáceres, Spain).

Citation: Tomás JF, Giraldo P, Lecumberri R, and Nistal S. POEMS syndrome with severe neurological damage clinically recovered with lenalidomide. Haematologica 2012;97(2):320-322. doi:10.3324/haematol.2011.041897

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Dispenzieri A. POEMS syndrome. Blood Rev. 2007;21(6):285-99.
2. Watanabe O, Maruyama I, Arimura K, Kitajima I, Arimura H, Hanatani M, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve. 1998;21(11):1390-7.
3. Gherardi RK, Bélec L, Soubrier M, Malapert D, Zuber M, Viard JP, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood. 1996;87(4):1458-65.
4. Dispenzieri A, Moreno-Aspitia A, Suarez GA, Lacy MQ, Colon-Otero G, Tefferi A, et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. Blood. 2004;104(10):3400-7.
5. Dispenzieri A, Klein CJ, Mauermann ML. Lenalidomide Therapy in a Patient with POEMS Syndrome. Blood. 2007;110(3):1075-6.
6. Sethi S, Tageja N, Arabi H, Penumetcha R. Lenalidomide therapy in a rare case of POEMS syndrome with kappa restriction. South Med J. 2009;102(10):1092-3.
7. Kuwabara S, Misawa S, Kanai K, Sawai S, Hattori T, Nishimura M, et al. Thalidomide reduces serum VEGF levels and improves peripheral neuropathy in POEMS syndrome. J Neurol Neurosurg Psychiatry. 2008;79(11):1255-7.
8. Jaccard A, Abraham J, Recher C, Dulery R, Guichard I, Haroche J, et al. Lenalidomide therapy in nine patients with POEMS syndrome [abstract]. Proceedings of the 51st Annual Meeting and Exposition of the American Society of Hematology 2009; December 5-8; New Orleans, LA: Abstract #3872.
9. Kuehne R, Goede J, Benz R, Stüssi G, Renner C. Immune modulatory drugs in POEMS syndrome [abstract]. Onkologie: Proceedings of the Joint Annual Conference of the German, Austrian, and Swiss Societies for Hematology and Oncology 2008; 31(Suppl 4): 186-7, Abstract # P538.
10. Ramirez G, Campos A, Rosell A, Queipo de Llano MP, García-Sánchez R, García-Delgado R, et al. Patient suffering from POEMS syndrome treated with lenalidomide plus dexamethasone [abstract]. Proceedings of the 14th Congress of the European Hematology Association 2009; June 4-7; Berlin, Germany: Abstract #1631.
11. Patel T, Moreno-Aspitia A. Alternative treatment for POEMS syndrome: A Lazarus response to lenalidomide [abstract]. Proceedings of the 50th Annual Meeting and Exposition of the American Society of Hematology 2008b; December 6-9; San Francisco, CA: Abstract #5205.