[3]Graduate Program in Biomedical Sciences, Faculty of Allied Health Sciences, Thammasat University, Pathumthani 12121, Thailand

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Keywords: α thalassemia, Hb Bart's, ELISA strip, monoclonal antibody

Correspondence: Luksana Makonkawkeyoon, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: international +66.53.945323 ext. 216. Fax: international 66.53.894031. E-mail: lmakonka@mail.med.cmu.ac.th

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References

1. Weatherall DJ, Clegg JB. The Thalassaemia Syndromes. 4th ed. Oxford, England: Blackwell Science Ltd; 2001.
2. Makonkawkeyoon L, Pharephan S, Makonkawkeyoon S. Production of a mouse hybridoma secreting monoclonal antibody highly specific to hemoglobin Bart's (γ^4). Lab Hematol. 2006;12(4):193-200.
3. Makonkawkeyoon L, Pharephan S, Tuntiwechapikul W, Makonkawkeyoon S. Application of monoclonal and polyclonal antibodies to Hb Bart's for the detection of α thalassemias. The Open Hematol J. 2009;3:11-7.
4. Bowden DK, Vickers MA, Higgs DR. A PCR-based strategy to detect the common severe determinants of α-thalassemia. Br J Haematol. 1992;81(1):104-8.
5. Smetanina NS, Huisman TH. Detection of α-thalassemia-2 (-3.7 kb) and its corresponding triplication ααα (anti-3.7 kb) by PCR: an improved technical change. Am J Hematol 1996;53(3):202-3.
6. Baysal E, Huisman TH. Detection of common deletional α-thalassemia-2 determinants by PCR. Am J Hematol. 1994; 46(3):208-13.
7. Makonkawkeyoon L, Sanguansermsri T, Asato T, Nakashima Y, Takei H. Rapid detection of chain termination mutations in the α-2 globin gene. Blood. 1993;82(11):3503-4.
8. Dawson B, Trapp RG. Basic & Clinical Biostatistics. 4th ed. International edition. Singapore: McGraw-Hill; 2004.
9. Sanguansermsri T, Phumyu N, Chomcuen S, Steger F. Screening for α-thalassemia-1 heterozygotes in expecting couples by the combination of a simple erythrocyte osmotic fragility test and a PCR-based method. Commun Genet. 1999;2(1):26-9.
10. Sirichotiyakul S, Tantipalakorn C, Sanguansermsri T, Wanapirak C, Tongsong T. Erythrocyte osmotic fragility test for screening of α-thalassemia-1 and β-thalassemia trait in pregnancy. Int J Gynecol Obstet. 2004;86(3):347-50.

Treatment with mycophenolate mofetil followed by recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes resistant to erythropoietin treatment

Anemia is present in most patients with low-risk MDS (LR-MDS).[1] Supportive treatment with transfusions was the final outcome of most of them, and transfusion-dependency is a prognostic factor for poor survival.[2] A number of studies have demonstrated that, overall, one third of LR-MDS responded to growth factor treatment. A score system was developed[3] which, according to transfusion requirements and serum erythropoietin levels, identifies cases with high or low probability of response.[3,4] One important aspect is that the response to growth factors is not maintained, with a median duration of 24 months. However, only 20% of patients had a response which lasted more than four years.[5]

One important aspect, frequently forgotten, is that many LR-MDS are elderly handicapped patients. In fact, the number of patients lost during treatments was as high as 20% in studies using Epo+/-G-CSF-G, which only required subcutaneous injections.[3,4]

Immunological disturbances have been proposed to be among the mechanisms involved in MDS pathogenesis. As in aplastic anemias, in MDS abnormal SMD stem cells trigger an immunological cellular response which in turn attacks abnormal stem cells causing more damage to the remaining stem cells. This finding is probably the physiological basis for anti-lymphocytic gammaglobulin +/- cyclosporine responses.[6] In MDS patients with trisomy 8, an expansion of a number of CD8 T-lymphocyte repertoires have been demonstrated, suggesting their involvement in the pathogenesis of MDS. In patients with refractory anemia, HLA-DR 15 and trisomy 8, the rate of response was 70%.[7,8] However, the immunosuppressive treatment is not well tolerated and requires hospital admission.[9]

The purpose of this work was to rescue LR-MDS patients who had lost their response to Epo, or to treat patients with low probability of response to Epo using the Scandinavian Score.[3] A therapeutical approach using sequentially immunosuppresion and growth factors was investigated. Mycophenolate mofetil and prednisone were used as immunosuppression because mycophenolate mofetil is given orally and is very well tolerated.[10]

The trial scheme (www.clinicaltrials.gov. Identifier: ML20559) used mycophenolate mofetil (Cell Cept) 1 g twice a day orally and oral prednisone 0.5 mg/Kg/d tapering prednisone to 10 mg/d. Mycophenolate mofetil and prednisone 10 mg were maintained to the end of the study. Response was evaluated at 12 weeks. In patients without major erythroid response, subcutaneous 30,000 U/week of recombinant human erythropoietin beta (Neorecormon) was added during six weeks. This was increased to 60,000 U/week in case of no major response following the IWG criteria.[11]

A total of 10 patients were treated (Table 1), including 8 cases that had received erythroid stimulating agents and had lost their response and 2 with high levels of serum erythropoietin. Seven of them were under transfusions. In one case the treatment was stopped because of pneumonia at two weeks. In 5 out of the 9 remaining cases, a response was observed; in 3 this was a major response (in one case under transfusions at the end of the study Hb was 96 g/L without transfusions, in one case with initial Hb of 81 g/L, Hb was 109 g/L after treatment, and in a case under transfusion final Hb was 97 g/L without transfusions). A minor response was seen in 2 patients (in one case the amount of transfusions was reduced from 6 units/month to 2 units, and in one case without transfusions Hb increased from 85 g/L to 101 g/L). Treatment was well-tolerated; 3 cases showed grade 1-2 diarrhea, in one case with diabetes mellitus an increase in diabetes treatment was required, and one case was admitted to hospital due to pneumonia.

In spite of the low number of cases included, this treatment with oral immunosuppresion followed by addition of growth factors, as antiapoptotic agents, obtained a good rate of response. It is worth remembering that the cases included were patients with few alternative treatments.

Table 1. Clinical characteristics and response to immunosuppression and growth factors treatment.

Pt/Diagnosis	Previous Treatment	Initial Hb/transf	Final Hb/transf	Changes Hb/transf 12 week-18week-24week	Response
1/ARS	r-hu-Epo	82/No	81/No		No
2/ARS	Darbepoetin	85/Yes	87/Yes		No
3/ARS	Darbepoetin	92/Yes	96/No	95/Y-83/N-96/N	Major
4/RCMD-S	r-hu-Epo	94/Yes	100/Yes		No
5/RCMD-S	No Epo > 300 u/L	81/No	109/No	99/N-96/N-109/N	Major
6/RCMD-S	No Epo > 300 u/L	87/Yes	-	-	Drop-out
7/ARS	Darbepoetin	77/Yes	78/Yes	-	No
8/ARS	Darbepoetin	71/Yes (6 u*)	82/Yes (2u)	83/Y(9u)-82/Y(2u)-82/Y(2u)	Minor (<50% transfusions)
9/ARS	Darbepoetin	86/Yes	97/No	89/Y-96/N-97/N	Major
10/RCMD-S	Darbepoetin	85/No	101/No	84/N-101/N-101/N	Minor

*Units per month. Pt: patient. ARS: refractory anemia with ring sideroblasts. RCMD-S: refractory cytopenia and multilinial dysplasia with ring sideroblasts. R-hu-Epo recombinant human erythropoietin. Transf: transfusions, Y: Yes, N:No. Hb in g/L.

This approach is easy to manage and well-tolerated, and does not require hospital admission.

In summary, using the scheme of oral immunosuppresion and growth factors, in 3 out of the 9 LR-MDS patients transfusions were no longer required. Obviously, larger studies should be carried out to confirm and validate this scheme of treatment. Immunosuppression and growth factors could be an alternative to new drugs that have appeared recently.

Angel F. Remacha, Beatriz Arrizabalaga, Javier Bueno, Juan Muñoz, Joan Bargay, and Carme Pedro

Complejo Hospitalario Toledo; Hospital de Cruces Baracaldo (Vizcaya); Hospital Vall d'Hebrón, Barcelona; Hospital Puerta del Mar, Cádiz; Hospital Son Llatzer, Palma de Mallorca, Hospital del Mar, Barcelona, Spain.

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Correspondence: Ángel F. Remacha, Complejo Hospitalario de Toledo, Hematology Department, Avenida Barber, Toledo, Spain. Phone: international +34.9.658249752. Fax: international +34.9.25269303. E-mail: aremacha@sescam.jccm.es

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References

1. Cazzola M, Mercuriali F, Brugnara C. Use of recombinant human erythropoietin outside the setting of uremia. Blood. 1997;89(12): 4248-67.
2. Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005;23(30): 7594-603.
3. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IM, Dybedal I, et al; Scandinavian MDS Group. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003;120(6):1037-46.
4. Remacha AF, Arrizabalaga B, Villegas A, Manteiga R, Calvo T, Julia A, Fernandez Fuertes I, Gonzalez FA, Font L, Junca J, del Arco A, Malcorra JJ, Equiza EP, de Mendiguren BP, Romero M. Erythropoietin plus granulocyte colony-stimulating factor in the treatment of myelodysplastic syndromes. Identification of a subgroup of responders. Haematologica. 1999;84(12):1058-64.
5. Jadersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. Blood. 2005;106(3):803-11.
6. Barrett AJ, Sloand E. Autoimmune mechanisms in the pathophisiology of myelodysplastic syndromes and their clinical relevance. Haematologica. 2009;94(4):449-51.
7. Shimamoto T, Ohyashiki K. Immunosuppressive treatments for myelodysplastic syndromes. Leuk Lymphoma. 2003;44(4):593-604.
8. Sloand EM, Mainwaring L, Fuhrer M, Ramkissoon S, Risitano AM, Keyvanafar K, et al. Preferential suppression of trisomy 8 compared with normal hematopoietic cell growth by autologous lymphocytes in patients with trisomy 8 myelodysplastic syndrome. Blood. 2005;106(3):841-51.
9. Steensma DP, Dispenzieri A, Moore SB, Schroeder G, Tefferi A. Antithymocyte globulin has limited efficacy and substantial toxicity in unselected anemic patients with myelodysplastic syndrome. Blood 2003;101(6):2156-8.
10. Kotb R, Pinganaud C, Trichet C, Lambotte O, Dreyfus M, Delfraissy JF, et al. Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: a single center preliminary study. Eur J Haematol 2005;75(1):60-4.
11. Cheson BD, Bennett JM, Kantarjian H, Pinto A, Schiffer CA, Nimer SD, et al; World Health Organization (WHO) international working group. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000; 96(12):3671-4.

Decitabine *versus* 5-azacitidine for the treatment of myelodysplastic syndrome: adjusted indirect meta-analysis

We read with great interest the systematic review and meta-analysis by Gurion *et al.* assessing the efficacy of hypomethylating agents (HMA) versus supportive care for the treatment of patients with myelodysplastic syndromes (MDS).[1] The meta-analysis included 4 randomized controlled trials (RCT). As the authors noted, we also performed a meta-analysis/systematic review on the same topic that included the same RCTs.[2,3] For the benefit of the medical community, it is important to see the reproducibility achieved by two groups working independently. Our