Original Article

Effect of Epoetin Alfa and Sodium Valproate in Patients with Myelodysplastic Syndrome

Seyed ashkan Hosseini[1*], Mahdi Tabarraee[1], Mojtaba Ghadiani[1]

[1] Department of Hematology and Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 17 July, 2019; Accepted: 08 November, 2019

Abstract

Background: Myelodysplastic syndrome (MDS) is an important precancerous disease leading to blood malignancies. Prompt diagnosis and treatment would result in better outcome in patients. Purpose of the study was to determine the effect of Epoetin Alfa and Sodium Valproate in patients with MDS.

Materials and Methods: In this interventional quasi-experimental study, 50 consecutive patients with MDS from Taleghani Hospital (Tehran, Iran) in 2016-2017 were enrolled. They underwent treatment for eight months with 10000 units per month from Epoetin Alfa plus 200 mg TDS from Sodium Valproate. The hematological response was determined according to the hemoglobin, platelet, and neutrophil.

Results: Hematological response was present in 68%. The packed cell treatment were decreased significantly (P=0.040) and 56% of patients had no receipt of packed cells after treatment.

Conclusion: It is concluded that Epoetin Alfa plus Sodium Valproate was effective in treatment of patients with Myelodysplastic syndrome and use of this combination therapy is recommended.

Keywords: Epoetin Alfa, Sodium Valproate, Myelodysplastic Syndrome

***Corresponding Author:** Seyed ashkan Hosseini, M.D, Department of Hematology and oncology department, Taleghani Hospital, Tehran, Iran. Email: ashkanho59@gmail.com

Please cite this article as: Hosseini S, Tabarraee M, Ghadiani M. Effect of Epoetin Alfa and Sodium Valproate in Patients with Myelodysplastic Syndrome. Novel Biomed. 2020;8(4):151-5.

Introduction

Myelodysplastic syndrome (MDS) includes a group of diseases with dysplastic alterations in myeloid, erythroid, and megacaryocyte subtypes[1] leading to cytopenia in some blood cells resulting in anemia and fatigue, neutropenia and infection, thrombocytopenia and bleeding[1,2]. Nearly fifty percent of cases may change to acute myeloid leukemia[1-3]. Erythropoietic stimulating agents (ESA) are usually used for treatment of MDS cases[4,5] have shown positive efficacy in comparison with supportive cases[6]. Usually these therapeutics have higher doses versus epoietin alfa ranging from 40000 to 80000 units weekly[7,8]. Low-dose ESA has lower response rate[9]. Some studies have used low dose epoietin alfa leading to lack of response and cotroverssies[10].

Valproic acid is a small chain fatty acid using as anti-convulsant for years and is effective on growth and differentiation of malignant cells[11]. Different studies have shown various results for valproic acid and in some studies, no effect on MDS and AML is seen[12]. The recent study about epoetin alfa found significant effect with high-dose[13]. In addition, valproic acid has shown up to forty percent efficacy in MDS cases and should be used simultaneously with other therapeutics[11]. Regarding these controversies, in this study the efficacy of Epoetin Alfa and Sodium Valproate combination in MDS patients was assessed.

Methods

In this interventional quasi-experimental study, 50 consecutive patients with MDS in Taleghani hospital (Tehran, Iran) in 2016-2017 were enrolled. Inclusion criteria were willing to incorporation in the study, easy to follow-up and blood-product dependent MDS. Exclusion criteria were previous successful treatments, death, and study termination. Local ethical committee approved the study and informed consent form received from all patients. Helsinki declaration was respected across the study.

They underwent treatment for eight months with 10000 units per month from Epoetin Alfa plus 200 mg TDS from Sodium Valproate. Valproic acid for treatment of seizure leads to inhibition of enzymatic activity and HDAC inhibition[14,15]. Duration of treatment was eight months including both drugs. The hematological response was determined according to the hemoglobin, platelet, and neutrophil. In addition, transfusion times and volume was recorded from the first week.

Data analysis was done among patients with SPSS version 13.0 software. The used tests were Independent-Sample-T, Fisher, and Chi-Square and the P value less than 0.05 were considered significant.

Results

In this study, 32 out of 50 patients (64%) were male. The mean (standard deviation) age was 65.3 (7.7) ranging from 53 to 84 years. The mean (standard deviation) duration of disease was 3.03 (2.4) ranging from 1 to 12 years. MDS subtype was with multilinage and unilinage in 38 and 62 percent, respectively.

Hematological response rate was 68%. Also as shown in Figure 1, the used pack cells were reduced after treatment with significant difference (P=0.040) and no pack cell use seen in 56% of patients after treatment. As shown in Figure 2 and Figure 3, the hematological responding cases had higher mean age (P=0.019) and lower duration of disease (P=0.037). However, the age and MDS subtype had no effect on therapeutic response among the patients (P > 0.05).

Discussion

In this study the efficacy of Alfa epoietin plus valproic acid was assessed to attain definite results about efficacy of these insurance-accepted therapeutics for MDS cases and also decrease the controversies. We found response rate of 68 percent and significant reduction in pack cell use. In a study among transfusion-dependent MDS cases, ESA agents similarly had good efficacy[13]. In a study among 23 cases under treatment with valproic acid, the response rate was 44 percent this lower than our study but in congruence with our study and other studies[16,17]. A review study by Hellström-Lindberg et al[18] reported median response duration of 2 to 3 years. However, in

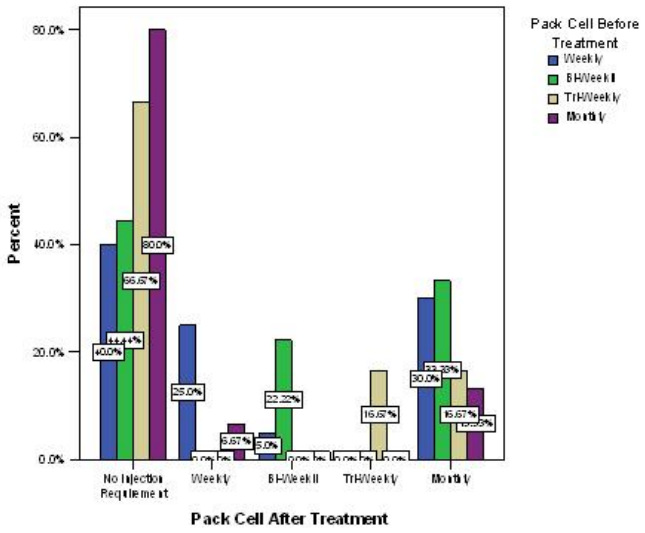

Figure 1. Pack cell use before and after treatment.

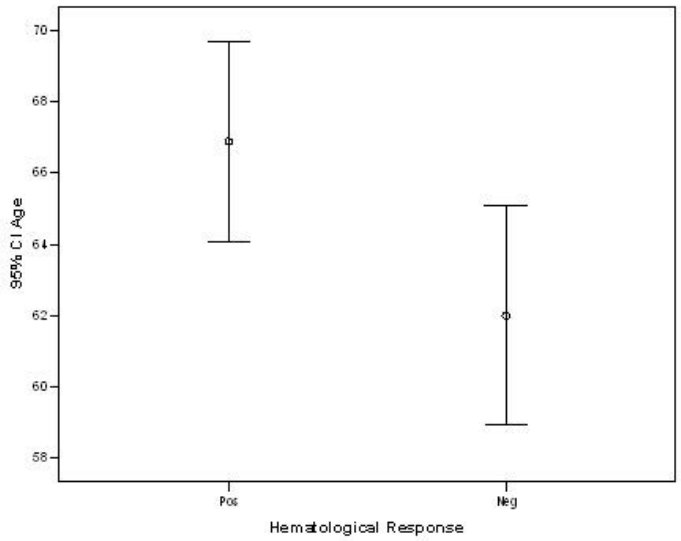

Figure 2. Mean age according to hematological response.

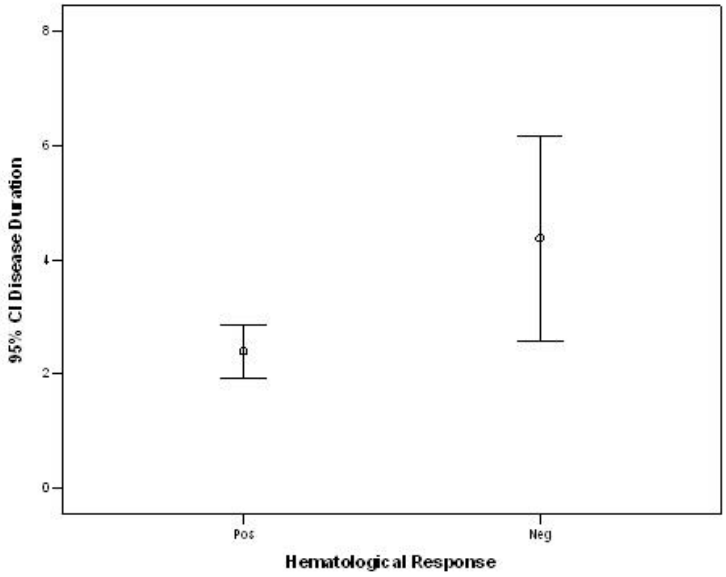

Figure 3. Mean duration of disease according to hematological response.

our study longer follow-up was impossible.

Toma et al[19] assessed 131 patients reported efficacy of 23 percent for erythropoietin alone rising to 39 percent in combination with other agents without significant increase in drug adverse effects as well as our study. Park et al[20, 21] assessed 1147 MDS patients and found efficacy and response of 61.5% with low response rate seen by second line treatment such as sodium valproate which was contrary to our study. Ornestein et al[22] declaimed good efficacy of combination therapy that was also approved in our study. In addition, Poloni et al[23] reported a case of MDS female patient with successful treatment outcomes with valproic acid and showed no recurrence of malignancy transformation that is similar to our study. Terpos et al[24] in the Italian co-operative study prolong administration of erythropoietin is conduce to long lasting erythroid RR in MDS patients that similar to our study.

According to our study, the average age of those who responded to treatment was higher, also, the mean duration of illness was higher in those who responded to treatment and there was no difference between sex and subtype of the disease.

Conclusion

It is concluded that Epoetin Alfa plus Sodium Valproate is effective in treatment of patients with Myelodysplastic Syndrome and use of this combination therapy is recommended. However further studies with larger sample population and multi-center sampling is required to attain results that are more definite and better therapeutic decision making in MDS cases with transfusion-dependent status.

Acknowledgment

None.

References

1. Faderl S. Kantarjian H. Myelodysplastic Syndromes. In: DeVita V, Lawrence T, Rosenberg S. Cancer Principles and Practice of Oncology. 9th edition. Lippincott Williams and Wilkins; Philadelphia, PA: 2011. p. 1988-96.
2. Silverman L. The Myelodysplastic Syndrome. In: Hong WK, Blast RC, Hait WN. Cancer Medicine. 8th edition. Shelton, CT: People's Medical Publishing House-USA; 2010. p. 1544-58.
3. Foran JM, Sekeres MA. Myelodysplastic Syndromes. In: Aberloff M, Armitage J, Niederhuber J, Kastan M, McKenna W. Abeloff's Clinical Oncology. 4th edition. Churchill Livingstone Elsevier; Philadelphia, PA: 2008. p. 2235-9.
4. Davidoff AJ, Weiss SR, Baer MR, Ke X, Hendrick F, Zeidan A, et al. Patterns of erythropoiesis-stimulating agent use among Medicare beneficiaries with myelodysplastic syndromes and consistency with clinical guidelines. Leuk Res. 2013; 37:675-80.
5. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Nat Cancer Inst. 2008;100:1542-51.
6. Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood. 2009;114:2393-400.
7. Steensma DP. Hematopoietic growth factors in myelodysplastic syndromes. Semin Oncol. 2011;38:635-47.
8. Musto P, Falcone A, Sanpaolo G, Bodenizza C, La Sala A, Perla G, et al. Efficacy of a single, weekly dose of recombinant erythropoietin in myelodysplastic syndromes. Br J Haematol. 2003;122:269-71.
9. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008;111:574-82.
10. Hoefsloot LH, van Amelsvoort MP, Broeders LC, van der Plas C, van Lom K, Hoogerbrugge H, et al. Erythropoietin-induced activation of STAT5 is impaired in the myelodysplastic syndrome. Blood. 1997;89:1690-700.
11. Kuendgen A, Strupp C, Aivado M, Bernhardt A, Hildebrandt B, Haas R, et al. Treatment of myelodysplastic syndromes with valproic acid alone or in combination with all-*trans* retinoic acid. Blood. 2004;104(5):1266-9.
12. Issa JP, Garcia-Manero G, Huang X, Cortes J, Ravandi F, Jabbour E, et al. Results of Phase II Randomized Study of Low-Dose Decitabine with or without Valproic Acid in Patients with Myelodysplastic Syndrome and Acute Myelogenous Leukemia. *Cancer.* 2015;121(4):556-61.
13. Duong VH, Baer MR, Hendrick F, Weiss SR, Sato M, Zeidan AM, et al. Variations in erythropoiesis-stimulating agent administration in transfusion-dependent myelodysplastic syndromes impact response. *Leuk Res.* 2015;39(6):586-91.
14. Acharya S, Bussel JB. Hematologic toxicity of sodium valproate. J Pediatr Hematol Oncol. 2000;22:62-5.
15. Gesundheit B, Kirby M, Lau W, Koren G, Abdelhaleem M. Thrombocytopenia and megakaryocyte dysplasia: an adverse effect of valproic acid treatment. J Pediatr Hematol Oncol. 2002;24(7):589-90.
16. Kuendgen A, Knipp S, Fox F, Strupp C, Hildebrandt B, Steidl C, et al. Results of a phase 2 study of valproic acid alone or in combination with all-trans retinoic acid in 75 patients with myelodysplastic syndrome and relapsed or refractory acute myeloid leukemia. Ann Hematol. 2005;84:61-6.
17. Kuendgen A, Bug G, Ottmann OG, Haase D, Schanz J, Hildebrandt B, et al. Treatment of poor-risk myelodysplastic syndromes and acute myeloid leukemia with a combination of 5-azacytidine and valproic acid. Clin Epigenetics. 2011;2(2):389-99.
18. Hellström-Lindberg E, van de Loosdrecht A. Erythropoiesis stimulating agents and other growth factors in low-risk MDS. Best Pract Res Clin Haematol. 2013;26(4):401-10.
19. Toma A, Kosmider O, Chevret S, Delaunay J, Stamatoullas A, Rose C, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia. 2016;30(4):897-905.
20. Park S, Greenberg P, Yucel A, Farmer C, O'Neill F, De Oliveira Brandao C, et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. Br J Haematol. 2019184(2):134-60.
21. Park S, Hamel JF, Toma A, Kelaidi C, Thépot S, Campelo MD, et al. Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents. J Clin Oncol. 2017; 35(14):1591-7.
22. Ornstein MC, Mukherjee S, Sekeres MA. More is better: combination therapies for myelodysplastic syndromes. Best Pract Res Clin Haematol. 2015;28(1):22-31.
23. Poloni A, Costantini B, Mariani M, Leoni P. Valproic acid for the treatment of low-risk myelodysplastic syndromes: A case report and a

review of the literature. Leuk Res Rep. 2013; 2(2):44-6.
Terpos E, Mougiou A, Kouraklis A, et al. Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: A phase II trial in 281 patients. Br J Haematol.. 2002;118:174–8.