RESEARCH ARTICLE

Neutrophil to Lymphocyte Ratio - Not an Independent Prognostic Factor in Patients with the Myelodysplastic Syndrome

Sema Akinci[1], Kamile Silay[2], Arife Ulas[3], Tekin Guney[1], Tuba Hacibekiroglu[1], Abdulkadir Basturk[1], Muhammed Bulent Akinci[3], Afra Alkan[4], Imdat Dilek[5]

Abstract

Purpose: Neutrophil-to-lymphocyte ratio (NLR) was evaluated as a potential prognostic factor in patients with myelodysplastic syndrome (MDS). Materials and Methods: Between December 2009 and April 2014, 14 female (35%) and 26 male (65%) MDS patients who were followed up in our hematology clinic were included in the study for NLR during diagnosis. Division was into two groups according to the NLR, and the correlation with mortality was evaluated. The prognostic significance of NLR regarding treatment outcome was also evaluated with adjustment for known confounding risk factors. Results: The mortality rate of the patient group was 55%, and median survival was 18 months. There was no significant correlation between mortality and NLR at a median value of 1.8 (p=0.75). Thrombocytopenia was observed to increase mortality (p=0.027), and there was a significant correlation between mortality and pancytopenia (p=0.017). Conclusions: This first study of NLR and mortality did not show any significant correlation . In centres with limited access to genetic evaluation for the presence of pancytopenia and/or thrombocytopenia at the time of diagnosis, a platelet level less than 50×10^9/l may be poor prognostic markers in MDS patients.

Keywords: Myelodysplastic syndrome - neutrophil/lymphocyte ratio - cytopenia - prognosis

Asian Pac J Cancer Prev, **15 (24)**, 10883-10885

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous clonal stem cell disease with a potential of progression to acute leukaemia; it manifests with inadequate hematopoiesis and the presence of cytopenias (Bejar et al., 2013). Clinically, patients may be asymptomatic or present with findings such as infections due to cytopenia, lassitude, and bleeding. Complete blood counts often reveal normocytic or macrocytic anaemia, and neutropenia or thrombocytopenia may accompany it.

Current classifications that include cytogenetic evaluations, such as the International Prognostic Scoring System and the World Health Organisation Prognostic Scoring System, are used in MDS risk classification (Kantarjian et al., 2008; Greenberg et al., 2012). In MDS patients, factors related to the nature of the disease and also personal characteristics may have affect mortality (Foran et al., 2012). Prognostic factors related to the nature of the disease are presence of myeloblasts, presence of cytopenia, karyotype, molecular mutations, fibrosis, transfusion dependence and iron overload, B2 microglobulin, lactate dehydrogenase, and albumin levels (Buesche et al., 2008; Wang et al., 2009; Mittelman et al., 2010; Della et al., 2011). Personal characteristics have been reported as age, performance status, comorbidities, smoking, obesity, and immune surveillance (Thiele et al., 2005; Naqvi et al., 2011).

With growing evidence on the role of inflammation in cancer biology, the systemic inflammatory response has been postulated as having prognostic significance in a wide range of different cancer types. The relative difference in the neutrophil and lymphocyte counts, the neutrophil-to-lymphocyte ratio (NLR), has attracted the interest of investigators as an emerging systemic inflammatory marker. A high preoperative or pretreatment NLR was identified as an independent prognostic factor associated with poor survival in various cancers, including breast cancer, colon cancer, lung cancer, and mesothelioma (He et al., 2014; Kemal et al., 2014). The pathogenesis and progression of the disease may be correlated to ovarian cancer; prognosis was found to be correlated with tumour volume in metastatic renal cell carcinoma, and there are reports that NLR may be a negative prognostic marker in thyroid carcinoma (Kim et al., 2013). In diffuse large B cell lymphoma cases, high NLR is considered as a poor prognostic factor. In addition, studies in multiple myeloma cases suggest that NLR at the time of diagnosis may be a simple, and inexpensive prognostic factor to assess clinical outcomes in multiple myeloma patients (Kelkitli et al.,

*[1]Department of Hematology, Ankara Ataturk Training and Research Hospital, [2]Department of Geriatrics, [3]Department of Oncology, [4]Department of Biostatistics, [5]Department of Hematology, Yildirim Beyazit University, Ankara, Turkey *For correspondence: sbakinci@hotmail.com*

2013; Troppan et al., 2014).

This study was planned in order to identify prognostic factors of MDS by using findings, including NLR, at the time of diagnosis in centres with limited access to genetic investigations.

Materials and Methods

Forty patients with MDS, comprising 14 females (35%) and 26 males (65%), who were followed up in our hematology clinic between 2009 and 2014 were included in the study. At the time of diagnosis, hemogram parameters (hemoglobin, leucocyte (lymphocyte and neuthrophil) and platelet count were noted and the NLR calculated. Since the total number of patients was low, a median value for NLR was used to assess the correlation between mortality and NLR. Cases with thrombocytopenia were further classified based on an upper limit of 50×10^9/l. Patients were classified according to the presence of bicytopenia or pancytopenia. Survival estimates of the patients were calculated starting from the diagnosis date until death due to disease or any other cause.

SPSS vers. 20 was used for the analyses. Kaplan-Meier analysis was used in statistical comparisons between mortality and other parameters. The correlation between the variables was considered significant at $p<0.05$.

Results

The median age of the patients was 70 years. Hemogram parameters and other laboratory values are summarized in Table-1.

The mortality assessment using a median NLR value of 1.8 showed no significant correlation (p=0.75). In our study, mortality rate was 55%, and median survival was 18 months. Twenty-four of the cases (60%) were found in patients over 65-years old; 39 of the patients (97.5%) had anemia, 25 (63.5%) leukopenia, 23 (57.5%) thrombocytopenia, and 13 (32.5%) neutropenia. The median hemoglobin value was 8 g/dl. The correlation between thrombocytopenia ($<150\times10^9$/l) and mortality was significant (p=0.027). Survival analyses results are summarized in Table-2. Sixteen (40%) patients had bicytopenia. Based on the bicytopenia classification at the time of diagnosis, six patients had anemia-leukopenia (15%), and five patients had anemia-thrombocytopenia (12.5%). There was no significant correlation between bicytopenia and mortality. Twenty-two of the MDS patients (55%) had pancytopenia; there was a significant correlation between pancytopenia and mortality (p=0.017).

Table 1. Hemogram Parameters and Other Laboratory values in MDS Patients

	N	min	max	mean	median	SD
Age	40	42	89	68,5	70	11,8
hemoglobin (g/dl)	40	5	13,1	8,2	8	1,9
leukocyte	40	0,6	20	4,7	3,3	3,6
thrombocyte	40	5	504	166	130	127,1
MCV (fL)	40	63,8	127,4	94,6	90,7	14,7
MPV	40	6,6	12,7	9,6	9,7	1,8
NLR	40	0,1	5,9	1,9	1,8	1,2
ferritin	40	13,9	2000	425,2	277,7	468,4
vit B12	40	63	1745	527,7	367,7	424,4
folate	40	3,2	20	7,9	6,3	4,7

Table 2. Survival Analysis Results in MDS Patients

Factor	Sayı (%)	P value
Thrombocytopenia(PLT<150x10^9/l)	23 (57.5%)	0.027
Thrombocytopenia (PLT<50x10^9/l)	7 (17.5%)	0.001
pancytopenia	22 (55.0%)	0.017

Discussion

In our study, there was no correlation between mortality and NLR in MDS cases. In the pathogenesis of MDS, there may be functional abnormalities of blood cells along with cytopenias affecting all hematopoietic cell lineages. Thus, calculating just the NLR may not be sufficient as a prognostic factor, and the presence of functional abnormalities in MDS patients should be taken into consideration.

MDS encompasses a series of hematological conditions characterized by chronic cytopenias (anemia, neutropenia, thrombocytopenia) accompanied by abnormal cellular maturation (Bejar et al., 2013). As a result, patients with MDS are at risk for symptomatic anemia, infection, and bleeding as well as progression to acute myeloid leukaemia, which is often refractory to standard treatment.

In hemograms of MDS cases, normochromic and normocytic anemia are almost always detected, but the frequency of neutropenia and thrombocytopenia vary. More than half of patients present with pancytopenia at the time of diagnosis. Isolated anemia is not rare, <5% of patients may have isolated neutropenia, thrombocytopenia, or monocytosis without anemia (Parnes et al., 2010; Chen et al., 2012). In our study, red blood cells of the patients were normocytic (mean MCV 94.6±14.7). With one exception, all patients (97.5%) had anemia. The case without anemia presented with isolated thrombocytopenia. In half of the patients with anemia, haemoglobin was <8 g/dl, and RBC replacement was required in these patients. There were seven MDS cases with thrombocytopenia $<50\times10^9$/l. In four of these, platelet transfusion was needed. Fifty-five percent of patients had pancytopenia, and 40% had bicytopenia. Thrombocytopenia and leucopenia have almost never been encountered as a bicytopenia pair, thus the almost absolute presence of anemia in MDS patients is a prominent finding. Isolated anemia was 20%, while isolated leucopenia and thrombocytopenia were 2.5% each; these findings are in agreement with reported studies. Studies suggest that refractory or severe thrombocytopenia$<30\times10^9$/l is a poor prognostic factor (Breccia et al., 2010; Gonzalez-Porras et al., 2011). We found that the presence of thrombocytopenia and a platelet count $<50\times10^9$/l both had an impact on mortality as poor prognostic factors. Thrombocytopenia is the main component increasing the mortality rate in the case of pancytopenia.

In conclusion, the correlation of mortality and NLR was investigated for the first time in MDS cases and was found to be statistically insignificant. Even though anemia

has no statistically significant effect on mortality, it is the most frequently encountered (97.5%) abnormality in MDS. Thrombocytopenia is the essential component increasing the mortality rate in the case of pancytopenia. Based on our findings, the presence of pancytopenia and/or thrombocytopenia (platelets <50×109/l) at the time of diagnosis in MDS patients could be used as poor prognostic markers..

References

Bejar R (2013). Prognostic models in myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program*, **2013**, 504-10.

Breccia M, Latagliata R, Cannella L, et al (2010). Refractory cytopenia with unilineage dysplasia: analysis of prognostic factors and survival in 126 patients. *Leuk Lymphoma*, **51**, 783.

Buesche G, Teoman H, Wilczak W, et al (2008). Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. *Leukemia*, **22**, 313.

Chen YD, Xu ZF, Cui R, et al (2012). A preliminary study of prognostic value of thrombocytopenia in patients with primary myelodysplastic syndromes. *Zhonghua Xue Ye Xue Za Zhi*, **33**, 532-5.

-Della Porta MG, Malcovati L, Strupp C, et al (2011). Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica*, **96**, 441-9.

Foran JM, Shammo JM (2012). Clinical presentation, diagnosis, and prognosis of myelodysplastic syndromes. *Am J Med*, **125**, 6-13.

Greenberg PL, Tuechler H, Schanz J, et al (2012). Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*, **120**, 2454-65.

Gonzalez-Porras JR, Cordoba I, Such E, et al (2011). Prognostic impact of severe thrombocytopenia in low-risk myelodysplastic syndrome. *Cancer*, **117**, 5529.

He WZ, Jiang C, Yin CX, et al (2014). Prognostic model built on blood-based biomarkers in patients with metastatic colorectal cancer. *Asian Pac J Cancer Prev*, **15**, 7327-31.

Kantarjian H, O'Brien S, Ravandi F, et al (2008). Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. *Cancer*, **113**, 1351.

Kelkitli E, Atay H, Cilingir F, et al (2013). Predicting survival for multiple myeloma patients using baseline neutrophil/lymphocyte ratio. *Ann Hematol*, **93,** 841-6.

Kemal Y, Yucel I, Ekiz K, et al (2014). Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. *Asian Pac J Cancer Prev*, **15**, 2651-4.

Kim JY, Park T, Jeong SH, et al (2013). Prognostic importance of baseline neutrophil to lymphocyte ratio in patients with advanced papillary thyroid carcinomas. *Endocrine*, **46**, 526-31.

Mittelman M, Oster HS, Hoffman M, and Neumann D (2010). The lower risk MDS patient at risk of rapid progression. *Leuk Res*, **34**, 1551-5.

Parnes A, Nikiforow S, Berliner N, Vanasse GJ (2010). Single nucleotide polymorphisms in the human TNF gene are associated with anaemia and neutropenia in a cohort of patients with de novo myelodysplastic syndrome. *Br J Haematol*, **150**, 700.

Thiele J, Kvasnicka HM, Facchetti F, et al (2005). European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica*, **90**, 1128.

Troppan K, Deutsch A, Gerger A, et al (2014). The derived neutrophil to lymphocyte ratio is an independent prognostic factor in patients with diffuse large B-cell lymphoma. *Br J Cancer*, **110**, 369-74.

Wang R, Gross CP, Halene S, Ma X (2009). Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes. *Leuk Res*, **33**, 1594-1598.