Department of Pharmacy[1], Kohka Public Hospital, Shiga; Department of Pharmacy[2], Ogaki Municipal Hospital, Gifu, Japan

Risk factors for neutropenia with lenalidomide plus dexamethasone therapy for multiple myeloma

Y. Mitani[1], E. Usami[2], M. Kimura[2], T. Nakao[2], K. Okada[2], T. Matsuoka[2], T. Kokuryou[1], T. Yoshimura[2], M. Yamakawa[1]

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Yasuhiro Mitani, Department of Pharmacy, Kohka Public Hospital, 1256 Matsuo, Minakuchi-cho, Kohka-shi, Shiga, 528-0074, Japan
resp591@yahoo.co.jp

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Neutropenia may develop as an adverse event in patients with multiple myeloma receiving lenalidomide (LEN) plus dexamethasone (DEX) therapy. In the present study, we examined the risk factors associated with grade 3/4 neutropenia during the first cycle of LEN plus DEX therapy. We observed that hemoglobin level (≤ 8.5 g/dl) was a significant risk factor for grade 3/4 neutropenia during the first cycle of therapy (odds ratio: 19.40; 95% confidence interval: 2.68–141.00; $p < 0.01$). Thus, our findings suggest that determining the hemoglobin level could be useful in the risk management for neutropenia in patients receiving LEN plus DEX therapy.

1. Introduction

Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by the clonal proliferation of malignant plasma cells in the bone marrow microenvironment, the presence of monoclonal protein in blood or urine, and associated organ dysfunction (Palumbo et al. 2011). In recent years, the treatment outcomes of multiple myeloma have markedly improved as a result of the introduction of new drugs such as bortezomib (BOR), which is a proteasomal inhibitor, as well as thalidomide (THAL) and lenalidomide (LEN), which are immunomodulatory drugs (IMiDs) (Richardson et al. 2005; Dimopoulos et al. 2009). LEN was approved for use in relapse/refractory cases in Japan in 2010, and is often used with dexamethasone (DEX) in the clinical setting. However, the administration of LEN frequently results in the development of neutropenia; in fact, Dimopoulous et al. (2009) reported that the frequency of grade 3/4 neutropenia in patients receiving LEN plus DEX treatment was 35.4 %. Moreover, the occurrence of neutropenia as a result of cancer chemotherapy increases the likelihood of infection, which could be fatal if appropriate antibiotic treatment is not initiated immediately (Lin et al. 2008). Therefore, the risk management of neutropenia is important in many elderly people receiving treatment for multiple myeloma. Moreover, Dimopoulous et al. (2014) reported that the exposure adjusted incidence rate (EAIR) of grade 3/4 neutropenia among patients who receive long-term benefits of LEN plus DEX therapy (progression-free survival ≥3 years) was low, and hence, it is likely that the development of the grade 3/4 neutropenia has an influence on the duration of treatment.

In the present study, we retrospectively assessed the risk factors of patients who developed grade 3/4 neutropenia during the first cycle of LEN plus DEX therapy.

2. Investigations and results

2.1. Patient background

From the 52 patients who received LEN plus DEX therapy, we excluded 3 patients who were diagnosed with neutropenia that was more severe than grade 3 during blood examination at the time of initiation of LEN plus DEX therapy and 2 patients who had insufficient information on the history of chemotherapy (Fig.). Accordingly, we assigned the 47 patients into a group wherein grade 3/4 neutropenia developed (neutropenia group) and another group wherein no neutropenia developed (non-neutropenia group) during the first cycle of therapy. The number of patients in the neutropenia group was 13 (27.7 %) and that in the non-neutropenia group was 34 (72.3 %).

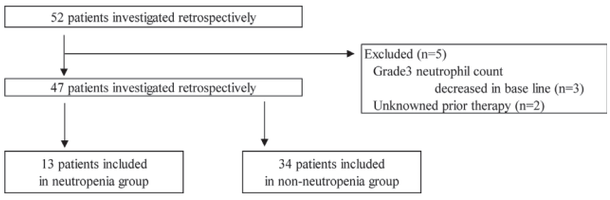

Fig. 1: Subject selection and the number of subjects analyzed

2.2. Investigation of the risk factors of neutropenia

Univariate analysis of 13 items as potential risk factors of neutropenia indicated a significant difference in the levels of neutrophils ($p = 0.04$) and hemoglobin ($p < 0.01$) (Table 1). With regard to the levels of neutrophils and hemoglobin, the area under the receiver operating characteristics curve was 0.794 and 0.835, whereas the cut-off value was 1,919/mm^3 and 8.5 g/dl, respectively. In the multivariate analysis, we also included factors with a p value of <0.2, including clinical stage (>II), LEN dose, and creatinine clearance rate (Table 2). As a result, we found that a hemoglobin level ≤ 8.5 g/dl was a significant risk factor for grade 3/4 neutropenia (odds ratio, 19.40; 95% confidence interval, 2.68–141.00; $p < 0.01$).

Table 1: Patient demographics and baseline characteristics

	Grade 3 or 4 neutropenia in first cycle		
Demographics and characteristics	with (n=13)	without (n=34)	P-value
Gender			
Male	6	17	
Female	7	17	1.00
Age , years			
Median	71	72	0.81
Range	65-88	50-90	

Demographics and characteristics	Grade 3 or 4 neutropenia in first cycle with (n=13)	without (n=34)	P-value
BMI (kg/m^2)			
Median	22.2	21.6	0.63
Range	14.2-27.5	13.7-27.1	
Clinical Stage (ISS)			
I	2	8	
II	5	18	
III	6	7	0.15
Date missing		1	
Myeloma protein class			
IgG	7	26	
IgA	3	3	
Bence-Jones protein	3	3	
IgD		2	
Prior PBSCT	4	7	0.47
No. of previous anti-myeloma therapy			
Median	3	2	0.22
Range			
1	5	16	
2	1	8	
≥3	7	10	
Dosage (first cycle)			
Lenalidomide, mg/day			
Median	10	25	0.13
Range	5-25	5-25	
Dexamethasone, mg/cycle			
Median	160	160	0.41
Range	40-480	80-480	
Total cycles			
Median	4	6	
Range	1-12	1-15	
Neutrophil, /mm^3			
Median	1,919	2,806	0.04
Range	1,001-4,160	1,130-8,597	
Hemoglobin, g/dl			
Median	8.0	11.0	<0.01
Range	6.5-11.4	6.3-13.9	
Platelets, ×10^4/μl			
Median	14.4	18.4	0.26
Range	3.7-18.6	5.4-59.3	
Total bilirubin, mg/dl			
Median	0.4	0.4	0.53
Range	0.3-0.6	0.1-1.8	
Creatinine clearance, ml/min			
Median	36.7	50.6	0.19
Range	9.9-85.5	5.4-127.0	

ISS, international staging system; BMI, body mass index; PBSCT, peripheral blood stem cell transplantation

Table 2: Multivariate analysis of the factors affecting grade 3 or 4 neutropenia during lenalidmide plus dexamethasone administration in first cycle (n=47)

Factor	OR	95% CI	P-value
Clinical stage (>II)	2.65	0.45-15.60	0.28
Lenalidomide dosage	1.00	0.86-1.16	1.00
Neutrophil (≤1,919/mm^3)	6.51	0.89-47.40	0.06
Hemoglobin (≤8.5g/dl)	19.40	2.68-141.00	<0.01
Creatinine clearance	0.97	0.93-1.02	0.21

OR, odds ratio; CI, confidence interval

3. Discussion

In the present study, we assessed the factors contributing to the high risk of neutropenia in patients receiving LEN plus DEX therapy. Although the mechanism through which LEN induces the development of neutropenia remains unclear, Pal et al. (2010) have indicated that the treatment of LEN causes PU.1 downregulation, which leads to the maturational block of neutrophil granulocytes and results in peripheral blood neutropenia (Pal et al. 2010).

The onset of grade 3/4 neutropenia was confirmed in 13 patients (27.7 %) during the first treatment cycle in our study, and the frequency of grade 3/4 neutropenia in all cycles was 48.9 %. In particular, Dimopoulos et al. (2009) reported that the frequency of grade 3/4 neutropenia in LEN plus DEX treatment was 35.4 %, which is inconsistent with that in the present study. Compared to the findings of Dimopoulous et al. (2009), the frequency of grade 3/4 neutropenia was low during the first treatment cycle, although the cumulative frequency in all cycles was high. Hence, the development of neutropenia in patients receiving LEN plus DEX therapy should be carefully monitored for a long duration.

We found that hemoglobin ≤ 8.5 g/dl was a risk factor of grade 3/4 neutropenia during the first cycle of LEN plus DEX therapy. Anemia is one of the characteristic clinical manifestations in multiple myeloma, and is defined by the by International Myeloma Working Group (IMWG. 2003) as "a hemoglobin level 2 g/dl below the lower limit of normal or hemoglobin < 10 g/dl" in myeloma-related organ or tissue impairment (end organ damage) due to the plasma cell proliferative process. We believe that the hemoglobin level of ≤ 8.5 g/dl could lead to the progression of the primary disease. Progression and relapse/refractory status of the primary disease are reported to be risk factors for the onset of grade 3/4 neutropenia (Lyman et al. 2005; Fortner et al. 2006). Hence, it is important to monitor the progress of the primary disease in order to manage grade 3/4 neutropenia in multiple myeloma therapy. In fact, multiple myeloma is characterized by various clinical manifestations including bone lesion and renal dysfunction, and we suggest that hemoglobin (≤ 8.5 g/dl)—identified as a risk factor in the present study—could serve as a useful indicator for understanding the progress of the primary disease and to manage grade 3/4 neutropenia.

In their examination of the predictors of severe neutropenia as a result of multiple myeloma treatment containing novel drugs (BOR/THAL/LEN), Palumbo et al. (2012) reported that neutrophil count <1000/mm^3 at baseline is an important risk factor. The introduction of new drugs enhances the options for treatment of multiple myeloma, and the treatment duration is usually long. Accordingly, several patients experience a delayed recovery of bone marrow activity due to the influence of previous treatment. In the present study, compared to the non-neutropenia group, the median number of previous treatments was high in the neutropenia group (neutropenia group: 3, non-neutropenia group: 2), although not significantly, and the neutrophil and platelet counts at baseline were low. These findings suggest that a previous history of treatment influences the bone marrow activity at baseline, and we believe that neutropenia should be managed while considering the previous history of treatment in LEN plus DEX therapy, when it is being chosen as a second line treatment option.

Moreover, LEN is excreted renally, and is associated with an increased risk of adverse events in patients with renal function disorders (Dimopoulos et al. 2010); however, a low level of renal function was not found to be a significant risk factor in this study. One reason for this finding may be because the physician and pharmacist maintained the dose setting appropriately while considering renal function. Thus, we suggest that maintaining an appropriate dose while considering renal function is important in the risk management of adverse events caused by overdose.

In conclusion, we assessed the risk factors of grade 3/4 neutropenia during the first cycle of patients receiving LEN plus DEX therapy. LEN plus DEX therapy is very useful and convenient in ambulatory patients. However, we believe that risk management of neutropenia should be ensured while considering the risk factors (hemoglobin ≤ 8.5 g/dl) in multiple myeloma therapy.

4. Experimental

4.1. Subjects and methods

We enrolled patients who received LEN plus DEX therapy from October 2010 to September 2015 at Ogaki Municipal Hospital (Ogaki, Japan). LEN was administered on days 1–21 of each 28-day cycle, and the dose was regulated depending on the renal function. Moreover, DEX was administered on days 1–4, 9–12, and 17–20, or on days 1, 8, 15, and 22.

We evaluated the patients' gender; age; body mass index (BMI); clinical stage (international staging system); myeloma protein class; history of autologous peripheral blood stem cell transplantation; history of prior therapy; number of doses (LEN, DEX); number of LEN plus DEX cycles; and neutrophil count, hemoglobin level, platelet count, total bilirubin level, and creatinine clearance at the time of chemotherapy initiation. The patients were divided into the neutropenia group and non-neutropenia group after assessing for the presence of grade 3/4 neutropenia from the medical charts. The neutropenia grade was assessed in accordance with the Japan Clinical Oncology Group/Japan Society of Clinical Oncology Japanese version of the Common Terminology Criteria for Adverse Events, v4.0.

4.2. Statistical analysis

Items were compared between the two groups using Fisher's exact test and Mann-Whitney's U test, and a significant difference was considered when the p value was <0.05. Moreover, using receiver-operator characteristic (ROC) curves, cut-off values were obtained for the continuous variables that showed a significant difference on univariate analysis. Thereafter, a logistic regression analysis was performed using these values as well as the variables with a p value of <0.2 on univariate analysis. All statistical analyses were performed with EZR (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

4.3. Ethical considerations

The present study was approved by the Institutional Review Board of Ogaki Municipal Hospital.

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