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Prediction of docetaxel monotherapy-induced neutropenia based on the monocyte percentage

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Abstract. We retrospectively reviewed the medical records of 32 chemonaïve patients with either breast, lung or prostate cancer, who were treated with docetaxel (DOC) monotherapy, and evaluated whether the proportion of peripheral blood monocytes was capable of predicting the occurrence of neutropenia following chemotherapy. In the granulocyte-colony stimulating factor (G-CSF) non-administration group, the monocyte percentage was inversely correlated with the decrease in neutrophils (P=0.01; corrected correlation coefficient, -0.71). The neutrophil count decreased by ≥30% in 7 of 8 patients with <5% monocytes, whereas it decreased by >30% in 1 of 6 patients with ≥5% monocytes (P=0.01). Three of 8 patients with <5% monocytes experienced grade 4 neutropenia, while in the group with ≥5% monocytes, 1 of 6 patients experienced grade 4 neutropenia. The frequency of grade 3 or 4 neutropenia was lower in patients with ≥5% monocytes than in patients with <5% monocytes, but the difference was not significant (P=0.41). Following G-CSF administration, grade 3 or 4 neutropenia had the tendency of lasting longer in patients with <5% monocytes than in those with ≥5% monocytes; however, the monocyte percentage was not correlated with the grade of neutropenia (P=0.34). The monocyte percentage following chemotherapy was inversely correlated with the decrease in neutrophils. The percentage of monocytes that are available in clinical practice may be predictive of neutropenia following chemotherapy. Our findings suggest that patients with <5% monocytes following DOC monotherapy are at risk of severe neutropenia and should be carefully monitored.

Introduction

The occurrence of neutropenia following the administration of cytotoxic anticancer drugs cannot be avoided. The probability of developing neutropenia varies for each individual regimen and is currently predicted on the basis of the physician's experience. It is known that an increase or decrease in monocytes occurs prior to changes in the neutrophil count. Hence, we often predict neutropenia from the fraction of monocytes; however, this is not a clear indicator. During outpatient chemotherapy, blood sampling is often only conducted on treatment days; therefore, physicians may overlook numerous cases of grade 4 neutropenia. In order to offer safe outpatient chemotherapy, at the Multidisciplinary Cancer Treatment Center of the Kanazawa Medical University Hospital, we monitor patients for adverse effects (e.g. hematologic toxicity) following initiation of the first chemotherapy when a regimen is used that could cause severe neutropenia. In this study, we retrospectively investigated blood sample data that were obtained following the first docetaxel (DOC) monotherapy, and tested whether we could predict neutropenia from the monocyte percentage.

Patients and methods

Patients. A total of 32 chemonaïve patients were identified on the basis of electronic medical records and retrospectively analyzed their blood samples. These patients had either breast, prostate or lung cancer. The patients were treated with DOC as the first outpatient chemotherapy at the Multidisciplinary Cancer Treatment Center of the Kanazawa Medical University Hospital from September 1, 2009 to December 28, 2010. Blood samples were obtained for monitoring the occurrence of neutropenia. On the basis of the blood sample data, 18 of 32 patients received granulocyte-colony stimulating factor (G-CSF). The backgrounds of the patients are shown in Tables I and II. The G-CSFs used were either filgrastim (75 μg) or lenograstim (100 or 150 μg). The status of G-CSF administration is shown in Table III. There were 7 male and 25 female patients, of which the mean age was 59.2 (range, 36-81) years. Breast cancer was diagnosed in 25 patients, lung cancer in 6 and prostate cancer in 1. Approval for our study was obtained from Kanazawa University Hospital.

Assessment of neutropenia. Blood samples obtained from each patient in the G-CSF administration group and in the G-CSF non-administration group were analyzed. Patients in the G-CSF non-administration group were classified as

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Table I. The background of the patients in the G-CSF non-administration group (group A).

Case	Carcinoma	Stage	Age (years)	Gender	PS (ECOG)	Dosage of docetaxel (mg/m^2)	Date of blood sampling (day)
1	Breast	0	36	Female	2	60	9,12
2	Breast	I	48	Female	0	60	8,12
3	Breast	IV	56	Female	2	60	8,10
4	Breast	I	48	Female	1	60	8,12
5	Breast	II A	60	Female	0	60	8,10
6	Breast	II A	54	Female	0	75	7,9
7	Lung	IV	81	Male	1	60	8,10
8	Breast	Unknown	54	Male	0	75	8,11
9	Breast	III A	47	Female	1	60	9,11
10	Lung	IV	55	Male	1	60	9,15
11	Lung	III A	81	Male	1	50	10,15
12	Breast	Unknown	43	Female	1	75	9,10
13	Prostate	IV	67	Male	1	60	11,14
14	Lung	III A	75	Male	1	50	11,15

G-CSF, granulocyte-colony stimulating factor; PS (ECOG), performance status (Eastern cooperative oncology group).

Table II. The background of the patients in the G-CSF administration group (group B).

Case	Carcinoma	Stage	Age (years)	Gender	PS (ECOG)	Dosage of docetaxel (mg/m^2)	Date of blood sampling (day)
15	Breast	II A	71	Female	1	50	14,15
16	Breast	III A	60	Female	0	60	9,11
17	Breast	II A	52	Female	0	60	10,13
18	Breast	I	53	Female	1	60	8,10
19	Breast	IV	69	Female	0	50	8,10
20	Breast	III	55	Female	1	75	10,11
21	Lung	IV	80	Male	1	60	8,11
22	Breast	II A	66	Female	1	60	8, 9
23	Breast	II B	54	Female	1	75	9,11
24	Breast	II B	67	Female	0	60	9,11
25	Breast	II B	64	Female	0	60	9,13
26	Breast	I	44	Female	Unknown	60	9,11
27	Breast	I	47	Female	1	75	9,10
28	Breast	IV	62	Male	1	60	8,15
29	Lung	IV	79	Male	1	60	9,13
30	Breast	III B	58	Female	1	75	9,10
31	Breast	II B	41	Female	Unknown	60	8,10
32	Breast	I	66	Female	1	60	8,10

G-CSF, granulocyte-colony stimulating factor; PS (ECOG), performance status (Eastern cooperative oncology group).

patients with <5% monocytes, 5-10% monocytes and >10% monocytes. Following treatment, blood samples were obtained between days 8 and 14. The rate of neutrophil decrease was calculated using the first and second neutrophil counts (between days 9 and 15). For example, if the first blood neutrophil count was 1500 μl and the second was 500 μl, the rate was calculated as: 1500-500/1500. Using the Spearman's rank correlation coefficient test, the degree of neutropenia and the monocyte percentage were examined for correlations in the G-CSF administration group and the G-CSF non-adminis-

Table III. Status of G-CSF administration.

Case	Type and dosage of G-CSF
15	Lenograstim 100 μg/day for 1 day
16	Filgrastim 75μg/day for 2 consecutive days
17	Lenograstim 100 μg/day for 2 consecutive days
18	Lenograstim 100 μg/day for 2 consecutive days
19	Filgrastim 75 μg/day for 2 consecutive days
20	Filgrastim 75 μg/day for 1 day
21	Filgrastim 75 μg/day for 2 consecutive days
22	Filgrastim 150 μg/day for 1 day
23	Filgrastim 75 μg/day for 2 consecutive days
24	Filgrastim 75 μg/day for 2 consecutive days
25	Filgrastim 75 μg/day for 2 consecutive days
26	Filgrastim 75 μg/day for 2 consecutive days
27	Filgrastim 75 μg/day for 1 day
28	Filgrastim 75 μg/day for 2 consecutive days
29	Filgrastim 75 μg/day for 4 consecutive days
30	Lenograstim 100 μg/day for 1 day
31	Filgrastim 75 μg/day for 2 consecutive days
32	Filgrastim 75 μg/day for 2 consecutive days

G-CSF, granulocyte-colony stimulating factor.

tration group. Neutropenia was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Results

G-CSF non-administration group

Correlation between the monocyte percentage and the rate of neutrophil decrease. The monocyte percentage was negatively correlated with the rate of neutrophil decrease (P=0.01; corrected correlation coefficient, -0.71).

Degree of neutropenia. In the group with <5% monocytes, a decrease in neutrophils of ≥30% was observed in 7 of 8 patients, whereas in the group with >5% monocytes, a decrease in neutrophils of >30% was only observed in 1 of 6 patients. This difference was significant (P=0.01). In the group with <5% monocytes, 3 of 8 patients experienced grade 4 neutropenia (38%), while in the group with >5% monocytes, 1 of 6 patients experienced grade 4 neutropenia (16%). The frequency of grade 3 or 4 neutropenia in patients with ≥5% monocytes was lower than that in the patients with <5% monocytes, but the difference was not significant (P=0.41) (Fig. 1).

Among the patients with >10% monocytes, there were only 2 cases (cases 13 and 14) in which the neutrophil count was higher in the second blood sample (Tables IV and V).

G-CSF administration group

Recovery from neutropenia following administration of G-CSF. In the G-CSF administration group, the neutrophil counts in all of the patients increased following treatment. In the group with <5% monocytes, grade 3 or 4 neutropenia persisted in 3 of 8 patients (38%), despite the administration of G-CSF. In the group with <5% monocytes, persistent grade 3 or 4 neutropenia appeared to occur more frequently, but there was no significant correlation between the monocyte percentage and the grade of neutropenia (P=0.34) (Fig. 2, Table VI).

Discussion

Due to of a lack of evidence, various guidelines do not recommend routine G-CSF administration for afebrile neutropenic patients (1). However, it has been reported that patients with

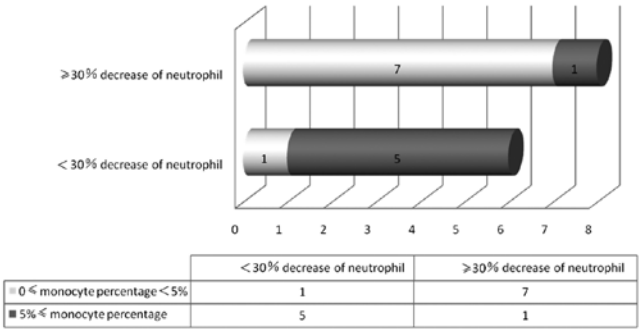
Table IV. Change in neutrophils in the G-CSF non-administration group.

Case	Monocyte percentage (%)	First neutrophil count (μl)	Second neutrophil count (μl)	Rate of neutrophil decrease	Second neutropenia grade
1	0.3	1600	250	0.843	4
2	1.0	1190	820	0.310	3
3	1.8	2510	2110	0.159	1
4	2.9	1190	820	0.311	2
5	3.3	1810	340	0.812	4
6	3.4	4110	980	0.762	3
7	3.7	370	120	0.676	4
8	4.1	1060	560	0.472	3
9	5.0	1550	1090	0.297	2
10	5.5	1210	1010	0.165	2
11	6.5	1350	780	0.422	3
12	8.4	630	490	0.222	4
13	8.9	1480	3010	-1.034	1
14	11.2	1260	1390	-0.103	2

G-CSF, granulocyte-colony stimulating factor.

Table V. Correlation between the monocyte percentage and the grade of neutropenia.

	0% ≤monocyte percentage <5%		5% ≤monocyte percentage		P-value
	n	%	n	%	
>30% decrease in neutrophil	7/8	87.5	1/6	16.7	0.01
Grade 3 or 4 neutropenia	6/8	75.0	2/6	33.3	0.41
	0% ≤monocyte percentage <5%		5% ≤monocyte percentage		
	n	%	n	%	
Grade 3 or 4 neutropenia	3/8	37.5	1/10	10.0	0.34



	Rate of neutrophil decrease		
	less than 30%	30%−70%	70% or more
0%≤monocyte percentage<5%	1	4	3
5%≤monocyte percentage <10%	4	1	0
10%≥monocyte percentage	1	0	0

Figure 1. Correlation between the monocyte percentage and decrease in the neutrophil count in the G-CSF non-administration group. G-CSF, granulocyte-colony stimulating factor.

high-grade neutropenia (<500 μl neutrophils) are at high risk of serious infections (2), and that once the patient presents with fever, there is a longer recovery period from neutropenia, even if G-CSF is administered (3). In addition, the prophylactic administration of G-CSF reduces the number of cases of febrile neutropenia and the number of hospitalizations associated with febrile neutropenia.

In general, G-CSF should not be routinely administered. However, the population of elderly cancer patients is steadily increasing and age is one of the risk factors for febrile neutropenia. Thus, if a patient is at high risk of developing febrile neutropenia, administration of G-CSF should be considered. Thus, it is extremely significant for clinicians to predict the degree of neutropenia following chemotherapy.

In our study, the type of carcinoma, dosage of DOC, type and dosage of G-CSF, and the days of blood sampling varied among the participants. The study was conducted retrospectively. Therefore, we should not regard the results of this study to be absolute. However, since there is a negative correlation between the degree of neutropenia and the percentage of monocytes, predicting neutropenia on the basis of the percentage of monocytes is suggested to be useful.

The results of our study have demonstrated that in the G-CSF non-administration group, when patients had less than 5% monocytes, a decrease in neutrophils of more than 30% was likely to occur. However, in the G-CSF non-administration group, a decrease in neutrophils of more than 30% was less likely to occur in patients with more than 5% monocytes. Using a backward calculation and considering that the neutrophil counts are expected to be the highest between days 7 and 10, patients in the G-CSF non-administration group with more than 5% monocytes and a neutrophil count of approximately 700 μl are not likely to develop grade 4 neutropenia. However, patients in the G-CSF non-administration group with less than 5% monocytes and a neutrophil count of approximately 700 μl are likely to develop grade 4 neutropenia. Nevertheless, it should be noted that there was 1 case in the G-CSF non-administration group with less than 5% monocytes in which the neutrophil count decreased from 1600 μl in the first blood sample to 250 μl in the second blood sample.

Table VI. Change in neutrophils in the G-CSF administration group.

Case	Monocyte percentage (%)	First neutrophil count (μl)	Second neutrophil count (μl)	Rate of neutrophil decrease	Second neutropenia grade
15	23.1	180	2900	-15.1	1
16	13.3	800	2410	-3.02	1
17	12.5	180	2560	-13.4	1
18	9.0	480	2050	-3.48	1
19	8.9	790	1580	-0.975	1
20	8.9	330	1400	-3.24	2
21	8.8	310	2810	-8.08	1
22	8.3	200	270	-0.35	4
23	5.4	550	1700	-2.09	1
24	5.0	330	1410	-3.27	2
25	4.8	330	3800	-10.5	1
26	4.7	430	3090	-8.19	1
27	4.8	250	720	-1.88	3
28	4.5	850	8910	-7.13	1
29	4.2	830	10000	-14.9	1
30	3.7	190	220	-0.158	4
31	2.8	210	240	-0.143	4
32	2.0	880	2810	-2.95	1

G-CSF, granulocyte-colony stimulating factor.

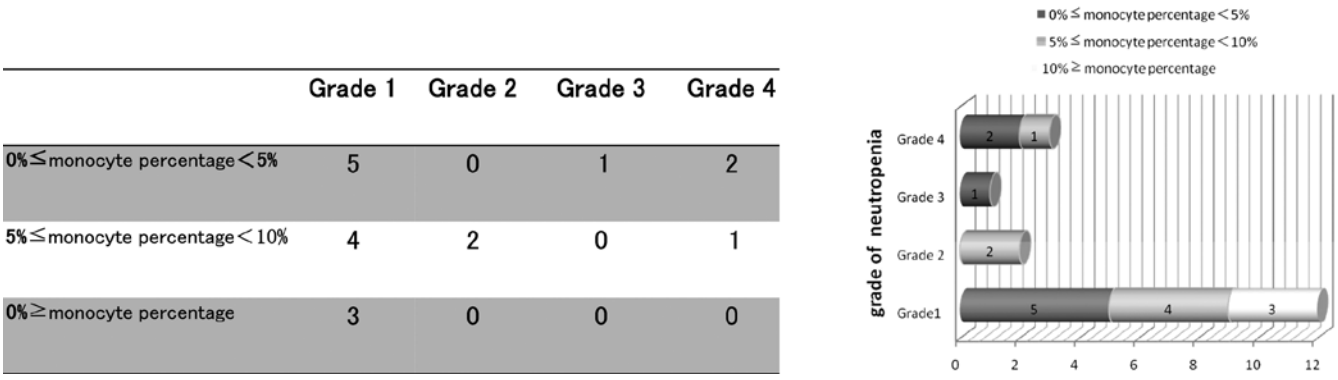


Figure 2. Correlation between the fraction of monocytes and the grade of neutropenia following G-CSF administration. G-CSF, granulocyte-colony stimulating factor.

As mentioned above, between days 7 and 10, when neutrophil counts are expected to be the highest, severe neutropenia is likely to occur in patients with less than 5% monocytes. In addition, we should recognize that even if G-CSF is administered, grade 4 neutropenia may persist if the percentage of monocytes is less than 5%. Thus, monitoring of neutropenic patients should be continued.

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