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Oral leukoplakia, a precancerous lesion of squamous cell carcinoma, in patients with long-term pegylated liposomal doxorubicin treatment

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Abstract

Pegylated liposomal doxorubicin (PLD) has a good safety profile, but long-term use has been associated with development of squamous cell carcinoma of the tongue and oral cavity (SCCTO) in some patients. The study objective was to estimate the prevalence of oral leukoplakia, a known precursor of SCCTO, in patients with ovarian cancer and long-term PLD use.

After approval of the institutional review board, medical record of 114 patients who were treated with PLD at our institution between January 2010 and December 2016 were retrospectively reviewed. All those patients have been referred for routine monitoring of oral mucositis every time before administration by a dentist. The patient characteristics included in the evaluation were age, smoking and drinking habits, the PLD dose and schedule, and presence or absence of oral leukoplakia and SCCTO at each oral examination. The relationships of the incidence of oral leukoplakia and patient characteristics were analyzed.

The median total PLD dose was 160 (range 40–1550) mg/m^2. Oral leukoplakia was seen in 6 (5.3%) patients. The median PLD dose, at the time of oral leukoplakia diagnosis, was 685 (range 400–800) mg/m^2. SCCTO was not found. Univariate analysis revealed that age, Brinkman index, and habitual drinking were not considered as risk factors for oral leukoplakia, and only total PLD dose (OR, 1.470; 95% CI, 1.19–1.91; $P < .001$) remained as a significant independent risk factor for oral leukoplakia. The ROC curve analysis indicated that the optimal cutoff value of the total PLD dose to predict development of oral leukoplakia was 400 mg/m^2. The sensitivity was 100% and the specificity was 88.8%. No patient discontinued PLD because of oral leukoplakia or SCCTO.

The 2 most important clinical observations were the occurrence of oral leukoplakia in patients with long-term PLD use and that the development of oral leukoplakia was related to a total cumulative dose ≥400 mg/m^2. Routine oral surveillance is recommended, particularly when the cumulative total dose exceeds 400 mg/m^2.

Abbreviations: CIs = confidence intervals, ORs = odds ratios, PLD = pegylated liposomal doxorubicin, ROC = receiver operating characteristic, SCCTO = squamous cell carcinoma of the tongue and oral cavity.

Keywords: chemotherapy, oral leukoplakia, pegylated liposomal doxorubicin, secondary cancer

1. Introduction

Pegylated liposomal doxorubicin (PLD) is approved for the treatment of Kaposi's sarcoma and recurrent ovarian cancer. PLD has a good safety profile,[1–3] but long-term use has been associated with development of squamous cell carcinoma of the tongue and oral cavity (SCCTO) in some patients.[4–11] Most of those patients were not smokers or excessive alcohol users and were not at risk of developing SCCTO.[4] Consequently, periodic oral evaluations are recommended for long-term PLD patients.[10] Since 2010, all patients treated with PLD at our institution have been referred for routine monitoring of oral mucositis each time before administration by a dentist. SCCTO has not been found in any patients, but oral leukoplakia, a known precursor of SCCTO has.

Oral leukoplakia occurs as a white patch or plaque of questionable risk that cannot be characterized clinically or pathologically as any other known disease.[13] It is not related to the presence or absence of dysplasia, but is considered a premalignant condition arising from chronic irritation of the oral mucosa. Smoking, alcohol consumption, chronic cheek biting, ill-fitting dentures, sharp teeth, syphilitic glossitis, candida infection, and vitamin A and B deficiencies have all been reported to increase the risk of oral leukoplakia.[14] Malignant transformation of oral leukoplakia is estimated to occur in 1% to 20% of patients over a period of 1 to 30 years.[15]

The study objective was to estimate the prevalence of oral leukoplakia in patients with ovarian cancer and long-term PLD use.

2. Materials and methods

The relationship of PLD treatment and the incidence of oral leukoplakia was retrospectively evaluated in a cohort of patients with histologically diagnosed ovarian, fallopian tube, and

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primary peritoneal cancer. After approval of the institutional review board, a search of electronic medical records identified 141 eligible patients who were treated at Cancer Institute Hospital of Japanese Foundation for Cancer Research between January 2010 and December 2016. Twenty-seven patients were excluded because of the lack of periodic checking for oral mucositis before each administration of PLD. The remaining 114 patients were included in this study. The patient characteristics included in the evaluation were age, smoking and drinking habits, the PLD dose and schedule, and presence or absence of oral leukoplakia and SCCTO at each oral examination. The presence of a smoking habit was "Yes" when the Brinkman index = [(Number of cigarettes smoked per day) × (Number of years smoked)] ≥100 and "No" if <100. The presence of a drinking habit was "Yes" when the patient drank "more than socially" and "No" when otherwise.

The characteristics of patients with and without oral leukoplakia were compared using the Chi-squared test for categorical variables, expressed as medians and range, and Student *t* test for continuous variables, expressed as means ± standard deviation. The relationships of the incidence of oral leukoplakia and patient characteristics were analyzed by logistic regression with the occurrence of leukoplakia as the dependent variable and patient age, smoking and drinking habits, and the total dose of PLD as explanatory variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The optimal cutoff value of the total PLD dose for the prediction of oral leukoplakia was calculated using receiver operating characteristic (ROC) curve analysis. Statistical analysis was performed using R version 3.3.1.[12] *P* values <.05 were considered statistically significant.

3. Results

The patient characteristics are shown in Table 1. The median age at the initial administration of PLD was 62 (range 25–86) years of age, 21 of 141 patients (18.4%) were smokers, and 47 (41.2%) were more than social drinkers. The median total PLD dose was 160 (range 40–1550) mg/m^2. Oral leukoplakia was seen in 6 (5.3%) patients; SCCTO was not found. Univariate analysis revealed that age, Brinkman index, and habitual drinking were not considered as risk factors for oral leukoplakia, and only total PLD dose (OR, 1.470; 95% CI, 1.19–1.91; $P < .001$) remained as a significant independent risk factor for oral leukoplakia (Table 2). The ROC curve analysis indicated that the optimal cutoff value of the total PLD dose to predict development of oral leukoplakia was 400 mg/m^2 (Fig. 1). The sensitivity was 100%, and the specificity was 88.8%. The characteristics of patients with oral leukoplakia are shown in Table 3 and Fig. 2. The median PLD dose, at the time of oral leukoplakia diagnosis, was 685 (range 400–800) mg/m^2, PLD was discontinued in 5 of the 6 patients because of disease progression. No patient discontinued PLD because of oral leukoplakia or SCCTO. The distribution of total PLD dose in patients with and without leukoplakia is shown in Fig. 2.

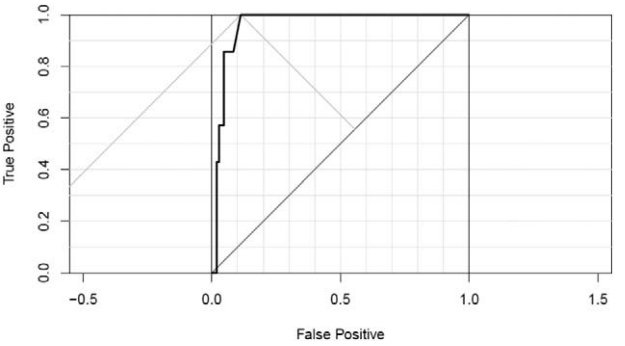

Figure 1. Receiver operating characteristic (ROC) curve analysis.

Table 1

Patient characteristics.

	n	Leukoplakia (%)	*P*
Age			
≤60	53	5 (9.4)	.15
>60	61	1 (1.6)	
Origin			
Ovary	99	6 (6.1)	.64
Fallopian tube	7	0 (0)	
Peritoneum	8	0 (0)	
FIGO stage			
I or II	13	1 (7.7)	.99
III or IV	101	5 (5.0)	
Histology			
Serous	25	2 (8)	.99
Nonserous	89	5 (4.5)	
Brinkman index			
≤100	93	5 (5.4)	.99
>100	21	1 (4.8)	
Habitual drinking			
Yes	47	1 (2.2)	.41
No	67	5 (7.5)	
Total dose of PLD, mg/m^2			
<400	95	0 (0)	<.05
≥400	19	6 (31.6)	

FIGO = International Federation of Gynecology, PLD = pegylated liposomal doxorubicin.

Table 2

Univariate analysis of risk factors for oral leukoplakia.

	OR	95% CI	*P*
Age			
≤60	0.160	(0.00820, 1.035)	.099
>60			
Brinkman index			
≤100	0.880	(0.0446, 5.86)	.91
>100			
Habitual drinking			
Yes	0.270	(0.0138, 1.75)	.24
No			
Total dose of PLD			
100 mg/m^2 increase	1.470	(1.19, 1.91)	<.001

CI = confidence interval, OR = odds ratio, PLD = pegylated liposomal doxorubicin.

Table 3

Characteristics of patients with oral leukoplakia.

Case	Age	Brinkman index	Habitual drinking	Dose at diagnosis of OL, mg/m^2	Total dose of PLD, mg/m^2
1	56	0	No	400	520
2	50	540	Yes	580	700
3	43	0	No	850	930
4	62	660	No	550	600
5	50	25	No	790	790
6	50	0	No	890	890

OL = oral leukoplakia, PLD = pegylated liposomal doxorubicin.

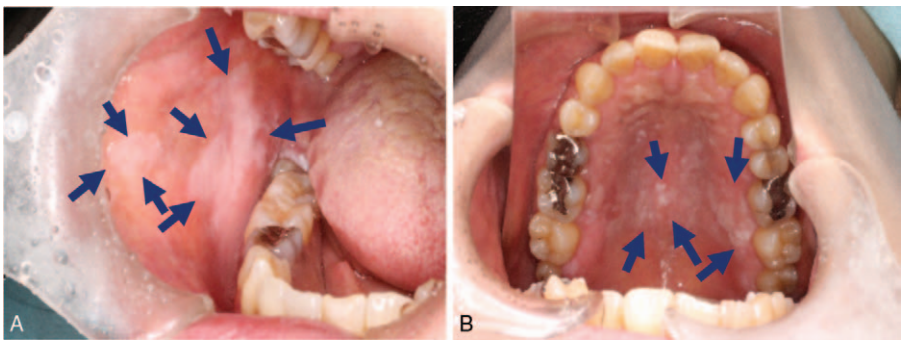

Figure 2. Oral leukoplakia appearing as a white patch.

4. Discussion

The 2 most important clinical observations were the occurrence of oral leukoplakia in patients with long-term PLD use and that the development of oral leukoplakia was related to a total cumulative dose ≥400 mg/m^2.

Six of the 19 patients given >400 mg/m^2 of PLD (31.6%) and 5 of the 12 (41.7%) given >500 mg/m^2 developed oral leukoplakia. As oral leukoplakia had not developed in any patients before PLD administration, the results may imply that PLD administration increased the incidence of oral leukoplakia in dose-dependent manner. Pharmacokinetic studies have shown that PLD has a higher plasma concentration and a much smaller volume of distribution than nonliposomal doxorubicin.[16] Liposomes accumulate in skin and mucous membranes and release doxorubicin and its metabolites over time. The prolonged exposure to doxorubicin is presumed to be the cause of an increased rate of secondary oral malignancies.[4] The limited available information indicates that the secondary oral tumors are less sensitive to conventional doses of radiation therapy than the primary tumors.[10] It is thus important to diagnose and treat SCCTO at an early stage. In general, older age, habitual smoking, and habitual drinking are thought to increase the risk of oral leukoplakia.[14] In this study cohort, general risk factors other than PLD administration were not considered as risk factors for oral leukoplakia. This fact shows that patients with oral leukoplakia in our study are associated with PLD administration. Early detection and management of oral leukoplakia, which is a precursor lesion of SCCTO, may improve the quality of life in patients with recurrent ovarian cancer.

This study was limited by its retrospective design, which is subject to selection bias. Secondly, as no patients developed SCCTO, the results provide little information about the incidence of, and time to develop, SCCTO in patients with oral leukoplakia. A cumulative PLD dose of 1260 to 3000 mg/body has previously been reported as required before developing SCCTO.[10]

In conclusion, the occurrence of 6 cases (5.3%) of oral leukoplakia in a cohort of patients with long-term PLD administration supports a recommendation of routine oral surveillance, especially when the cumulative total dose exceeds 400 mg/m^2. Under strict surveillance, patients with oral leukoplakia may continue treatment using PLD.

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