

Incidence of palmar-plantar erythrodysesthesia in pretreated and untreated patients receiving pegylated liposomal doxorubicin

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ABSTRACT

Aims and background. Association between pegylated liposomal doxorubicin-based regimens and palmar-plantar erythrodysesthesia have just been emphasized, whereas the relationship between previous treatment and palmar-plantar erythrodysesthesia is still a matter of discussion. We evaluate the relationship between previous chemotherapy treatments and the development of palmar-plantar erythrodysesthesia in patients receiving pegylated liposomal doxorubicin-based regimens.

Methods. Between January 2005 and November 2006, 92 patients received regimens including pegylated liposomal doxorubicin. Patients were divided into three groups based on pegylated liposomal doxorubicin dosing interval length, different dose chosen, and previous chemotherapy.

Results. Among pretreated patients receiving regimens including 30 mg/m² of pegylated liposomal doxorubicin repeated every three weeks, the incidence of palmar-plantar erythrodysesthesia was not significantly higher than in untreated patients receiving the same weekly schedule ($P = 0.4$). There was no difference in the incidence of palmar-plantar erythrodysesthesia between pretreated patients with regimens including 30 mg/m² of pegylated liposomal doxorubicin every three weeks and pretreated patients receiving 20 mg/m² of pegylated liposomal doxorubicin every two weeks ($P = 0.8$). The prevalence of palmar-plantar erythrodysesthesia observed in the untreated group exposed to 30 mg/m² every three weeks was comparable to that of the pretreated group receiving 20 mg/m² biweekly ($P = 0.3$). However, excluding all the patients who developed grade 1 palmar-plantar erythrodysesthesia, the incidence of grade 2 and 3 palmar-plantar erythrodysesthesia observed in pretreated patients receiving regimens including 20 mg/m² of pegylated liposomal doxorubicin biweekly was significantly higher than in untreated patients receiving 30 mg/m² of pegylated liposomal doxorubicin every three weeks ($P = 0.001$).

Conclusions. Our findings indicate that the pretreatment is not involved in the increased incidence of any grade palmar-plantar erythrodysesthesia. On the contrary, the study could suggest that the type of previous treatment may be an important factor in the development of more severe forms of palmar-plantar erythrodysesthesia.

Introduction

Palmar-plantar erythrodysesthesia (PPE) is a relatively frequent and often serious toxicity associated with pegylated liposomal doxorubicin (PLD)-based regimens¹⁻³. It has been suggested that, following local trauma associated with routine activities, PLD may extravasate from the deeper microcapillaries of the hands and feet and penetrate into the stratum corneum. Its accumulation may subsequently cause a local inflammatory tissue reaction. Moreover, there is evidence that PLD secretion with sweat is an important trigger of the condition¹.

Key words: palmar-plantar erythrodysesthesia, skin toxicity.

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PPE has been classified in four grades. Grade 1 is characterized by mild erythema, swelling, or desquamation not interfering with daily activities; skin toxicity increases until grade 4, characterized by a diffuse or local process which causes infectious complications or a bed-ridden condition.

The development of PPE has had a significant statistical correlation with half-life ($T_{1/2}$), whereas the correlation with dose intensity ($\text{mg}/\text{m}^2/\text{week}$ given during the first 2 or 3 cycles of treatment) did not appear to reach statistical significance⁴. PPE usually develops after two or more courses of treatment and is schedule-dependent, with shorter dosing intervals leading to increased frequency and severity of skin manifestations.

In the present study, we reviewed the impact of exposure to various chemotherapy regimens containing PLD on skin toxicity, specifically PPE, in a cohort of women with malignancies including ovarian cancer, breast cancer and endometrial cancer to evaluate whether a previous treatment could promote the development of PPE.

Material and methods

Between January 2005 and November 2006, we analyzed 92 patients retrospectively recruited from the Centro di Riferimento Oncologico (National Cancer Institute) at Aviano, Italy. All patients received chemotherapy regimens including PLD after obtaining written informed consent. Malignancies included ovarian cancer ($n = 73$), breast cancer ($n = 16$), endometrial cancer ($n = 2$) and ovarian cancer associated with breast cancer ($n = 1$).

All subjects had a performance status ≤ 2 , adequate renal function (serum creatinine $\leq 1.25 \times$ the upper normal limit), liver function (AST/ALT $\leq 3 \times$ the upper normal limit, bilirubin concentrations ≤ 1.25 the upper normal limit) and bone marrow function (neutrophil count $> 1,500/\mu\text{l}$ and platelet count $> 100,000/\mu\text{l}$). Toxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0⁵.

Patients were divided into three groups based on PLD dosing, interval length (biweekly or every three weeks), different dose chosen ($20 \text{ mg}/\text{m}^2$ or $30 \text{ mg}/\text{m}^2$), and previous chemotherapy (Table 1).

Group A included 51 pretreated patients with ovarian cancer ($n = 48$), endometrial cancer ($n = 2$) and ovarian cancer associated with breast cancer ($n = 1$) receiving regimens with $30 \text{ mg}/\text{m}^2$ of PLD every 3 weeks. Mean age was 59.9 years (range, 38-82). Altogether, patients received 299 PLD cycles of chemotherapy, with a median of 5.9 courses per patient (range, 3-12). Six patients had a dose reduction of PLD. Twenty-four of these patients were treated with PLD plus carboplatin, area under curve (AUC 5), 17 with PLD associated with gemcitabine ($1000 \text{ mg}/\text{m}^2$), and 8 with PLD plus cisplatin ($60 \text{ mg}/\text{m}^2$); in another two patients only PLD was administered.

Group B was composed of 23 untreated patients with ovarian cancer receiving $30 \text{ mg}/\text{m}^2$ of PLD every 3 weeks associated with carboplatin (AUC 5) according to the MITO 2 protocol. Mean age was 55.6 (range, 41-71). The patients received a median of 5.9 chemotherapy cycles (range, 5-6).

Group C included 18 pretreated patients with breast cancer ($n = 16$) and ovarian cancer ($n = 2$) receiving regimens including $20 \text{ mg}/\text{m}^2$ of PLD every two weeks. Mean age was 58.9 (range, 40-77). Two patients had a dose reduction of PLD. Altogether, the patients received 112 cycles of chemotherapy, with a median of 6.2 courses per patient (range, 3-12). Seventeen patients received PLD only, whereas in one patient PLD was associated with gemcitabine ($1000 \text{ mg}/\text{m}^2$).

The incidence of skin toxicity due to PLD-based regimens, specifically PPE, was compared in the three groups of PLD treated patients using two-sided Fisher's exact test as appropriate⁶, and the relative risk was estimated using odds ratio (OR). The 95% confidence interval (CI) for OR was calculated using Cornfield's method.

Results

The incidence and severity of PPE in the three groups based on PLD dosing interval length (2- or 3-weekly schedule), different dose chosen, and previous treatment are summarized in Table 1. There was no grade 4 skin toxicity. PPE of any grade was experienced in 41.3% of patients (38/92), whereas grades 2 and 3 PPE was observed in 16.3% (15/92). The median time to develop-

Table 1 - Subdivision into four groups based on PLD dosing interval length (2 or 3-weekly schedule) and previous treatment

Groups	Pretreatment	No.	PLD dose & schedule	Incidence of PPE, no. (%)				
				Grade 1	Grade 2	Grade 3	Grade 4	All grades
Group A	Heavily pretreated	51	$30 \text{ mg}/\text{m}^2$ q3 weeks	14 (27.5)	6 (11.7)	2 (3.9)	-	22 (43.1)
Group B	Not pretreated	23	$30 \text{ mg}/\text{m}^2$ q3 weeks	7 (30.4)	-	-	-	7 (30.4)
Group C	Heavily pretreated	18	$20 \text{ mg}/\text{m}^2$ q2 weeks	2 (11.2)	6 (33.3)	1 (5.5)	-	9 (50)

PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia.

ment of grades 2 and 3 PPE in pretreated patients receiving 30 mg/m² of PLD every three weeks was 3.8 (range, 3-5), whereas in those receiving 20 mg/m² of PLD biweekly it was 4.1 (range, 3-6).

Among pretreated patients receiving regimens including 30 mg/m² of PLD repeated every three weeks, the incidence of PPE was similar to that of untreated patients ($P = 0.4$; OR 1.73; CI 95%, 0.55-5.85) receiving the same schedule.

There was no significant difference in the incidence of PPE between pretreated patients exposed to 30 mg/m² of PLD every three weeks and pretreated patients receiving 20 mg/m² of PLD every two weeks ($P = 0.8$; OR 0.76; CI 95%, 0.22-2.57). Moreover, the prevalence of PPE observed in the untreated group exposed to 30 mg/m² every three weeks was comparable to that of the pretreated group receiving 20 mg/m² biweekly ($P = 0.3$; OR 0.44; CI 95%, 0.10-1.88).

Excluding by statistical analysis all the patients who developed grade 1 PPE, the occurrence of grades 2 and 3 PPE observed in pretreated patients receiving regimens including 20 mg/m² of PLD every two weeks was significantly greater than in untreated patients receiving 30 mg/m² of PLD every three weeks ($P = 0.001$; OR 0.0; CI 95%, 0.0-0.29).

Discussion

An association between PLD-based treatment and skin toxicity was originally reported in 1995⁷. Results of the various studies on the toxic skin effects due to PLD administration are not completely equivalent given the varying dose chosen, treatment schedules, and chemotherapy regimens^{2-4,8-9}.

Recently, a 14% incidence of PPE was reported in patients with ovarian cancer undergoing first-line chemotherapy consisting of PLD at a dose of 30 mg/m² on day 1 plus carboplatin (AUC 5) on day 1, repeated every 3 weeks. Only one patient (2%) had grade 3 PPE, and no delay due to PPE was recorded¹⁰.

In our study, PPE was observed in 7 of 23 (30.4%) patients who received a first-line regimen consisting of PLD, 30 mg/m² on day 1 associated with carboplatin (AUC 5) on day 1, repeated every 3 weeks. All 7 patients experienced grade 1 PPE. Therefore, these data are in accord with the safety and favorable toxicity of this dose and schedule of PLD.

However, in pretreated patients receiving 30 mg/m² of PLD repeated every 3 weeks, the incidence of grades 2 and 3 PPE was more frequently observed, occurring in 8 of 51 (15.7%) patients. Moreover, the high incidence of PPE was associated with short schedules. In the study of Sehouli *et al.*³, PPE of any grade was found in 30/64 (47.6%) patients with recurrent ovarian, peritoneal, or fallopian cancer. In all patients, previously treated with platinum and paclitaxel, PLD was administered at the

dose of 20 mg/m² every 2 weeks. Only three patients progressed to grade 3 (4.7%).

In accord with these data, we observed PPE of any grade in 9/18 (50%) pretreated patients receiving 20 mg/m² of PLD biweekly. Six of them (33.3%) experienced grade 2 PPE and only one progressed to grade 3 (5.5%).

However, the comparison between the prevalence of grades 2 and 3 PPE occurring in the pretreated group receiving PLD 20 mg/m² biweekly and that of the untreated group receiving PLD 30 mg/m² every three weeks showed a statistically significant difference.

These findings indicate that the pretreatment is not involved in the increased incidence of any grade PPE. On the contrary, our study could suggest that the type of previous treatment may be an important factor in the development and severity of grades 2 and 3 PPE. Interestingly, most of the patients who received regimens including 20 mg/m² of PLD repeated every two weeks and who developed grades 2 and 3 PPE had undergone more chemotherapeutic lines and chemotherapy regimens containing capecitabine, a drug able to predispose to the PPE syndrome. However, because of the small number of selected patients in the series, our data should be confirmed by further studies based on larger patient populations.

References

- Jacobi U, Waibler E, Schulze P, Sehouli J, Oskay-Ozcelik G, Schmook T, Sterry W, Lademann J: Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome? *Ann Oncol*, 16: 1210-1211, 2005.
- Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G: Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand foot' syndrome). *Ann Oncol*, 18: 1159-1164, 2007.
- Sehouli J, Oskay -Özcelik G, Kühne J, Stengel D, Hindenburg H-J, Klare P, Heinrich G, Schmalfeldt B, Mertens H, Camara O, Lichtenegge W: Biweekly pegylated liposomal doxorubicin in patients with relapsed ovarian cancer: results of a multicenter phase-II trial. *Ann Oncol*, 17: 957-961, 2006.
- Lyass O, Uziely B, Ben-Yosef R, Tzemach D, NI Heshing, Lotem M, Brufman G, Gabizon A: Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (doxil) in metastatic breast carcinoma. *Cancer*, 89: 1037-1047, 2000.
- National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) December 12, 2003.
- Fleiss JH: The measurement of interrater agreement. In: *Statistical Methods for Rates and Proportions* (Second Edn), John Wiley & Sons, New York, 1981.
- Uziely B, Jeffers S, Isacson R, Kutsch K, Wei-Tsao D, Yehoshua Z, Libson E, Muggia FM, Gabizon A: Liposomal doxorubicin antitumor activity and unique toxicities during two complementary phase I studies. *J Clin Oncol*, 13: 1777-1785, 1995.
- Alexopoulos A, Karamouzis MV, Stavrinides H, Ardavanis

- A, Kandilis K, Stavrakakis J, Georganta C, Rigatos G: Phase II study of pegylated liposomal doxorubicin (Caelyx®) and docetaxel as first-line treatment in metastatic breast cancer. *Ann Oncol*, 15: 891-895, 2004.
9. Gogas H, Papadimitriou C, Kalofonos HP, Bafaloukos D, Fountzilas G, Tsavdaridis D, Anagnostopoulos A, Onyenadum A, Papakostas P, Economopoulos T, Christodoulou C, Kosmidis P, Markopoulos C: Neoadjuvant chemotherapy with a combination of pegylated liposomal doxorubicin (Caelyx®) and paclitaxel in locally advanced breast cancer: a phase II study by the Hellenic Cooperative Oncology Group. *Ann Oncol*, 13: 1737-1742, 2002.
10. Pignata S, Scambia G, Savarese A, Breda E, Scillo P, De Vivo R, Rossi E, Gebbia V, Natale D, Del Gaizo F, Naglieri E, Ferro A, Musso P, D'Arco AM, Sorio R, Pisano C, Di Maio M, Signoriello G, Annunziata A, Perrone F: Safety of a 3-weekly schedule of carboplatin plus pegylated liposomal doxorubicin as first-line chemotherapy in patients with ovarian cancer: preliminary results of the MITO-2 randomized trial. *BMC Cancer*, 6:202, 2006.