The use of cod liver oil by patients receiving pegylated liposomal doxorubicin is associated with a lack of severe palmar-plantar erythrodysesthesia

M. Kanis[1], *M.D.*; J.P. Kesterson[2], *M.D.*; S. Lele[2], *M.D.*

[1]University at Buffalo School of Medicine, Buffalo, [2]Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY (USA)

Summary

Pegylated liposomal doxorubicin (PLD) is an effective and tolerable agent in the treatment of recurrent and refractory ovarian carcinoma. One of the most common dose-limiting toxicities of PLD is palmar-plantar erythrodysesthesia (PPE). We report a retrospective review of patients who took cod liver oil (CLO) while being treated with PLD at Roswell Park Cancer Institute. None of the patients required dose reduction, treatment interruption or discontinuation secondary to skin toxicity. No patient experienced grade 2 or greater PPE. The mechanism for the development of PLD-induced PPE is unknown. CLO may possibly mitigate it via decreased extravasation of PLD and/or by a blunting of the local inflammatory response. The effects of CLO should be further evaluated in a prospective, randomized trial, and attempts to elucidate the mechanism by which CLO may exert its effects should be pursued.

Key words: Pegylated liposomal doxorubicin; Palmar-plantar erythrodysesthesia; Cod liver oil.

Introduction

Pegylated liposomal doxorubicin (PLD) is an effective and tolerable agent in the treatment of recurrent and refractory ovarian carcinoma [1, 2]. One of the most common dose-limiting toxicities of PLD is palmar-plantar erythrodysesthesia (PPE). In a randomized phase III study comparing PLD to topotecan, PPE occurred in 49% of patients in the PLD arm [3]. PPE is characterized initially by dysesthesia of the hands and feet which progresses to edema with erythema with associated pain and subsequent fissure and ulcer development. These symptoms compromise the patient's ability to perform activities of daily living secondary to pain associated with grasping objects and/or walking.

The exact mechanism of PPE is unknown. PLD dose adjustments, oral pyridoxine, topical dimethylsulfoxide, steroids, and regional cooling have all been utilized in an attempt to prevent or treat PPE [4-8]. The aim of this study was to determine if cod liver oil (CLO) could prevent or mitigate PLD-induced PPE.

Materials and Methods

After obtaining institutional review board approval, a retrospective review of patients who took CLO while being treated with PLD at Roswell Park Cancer Institute was initiated. Eighteen patients met inclusion criteria. PLD was initiated at 40 mg/m^2 every 28 days when used as single-agent therapy or at 30 mg/m^2 every 28 days when used in combination with another agent. CLO was self administered. Patients had been instructed to take one capsule with meals, three times per day. Toxicities were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (Table 1). Patients were surveyed and examined at each clinic visit to assess their compliance with CLO, any associated side-effects as well as any PLD toxicity, including PPE.

Results

Eighteen patients had agreed to take CLO while on PLD. A total of 72 cycles of PLD were administered after initiation and continuation of CLO. The average number of cycles of PLD administered while on CLO was four (range: 2-8). No patients required dose reduction, treatment interruption or discontinuation secondary to skin toxicity. No patient experienced grade 2 or greater PPE. Of the 72 cycles administered, PPE was assessed as absent for 51 cycles and grade 1 for 21 cycles. Half of the patients (9) were assessed as having no evidence of PPE throughout their concurrent use of CLO and PLD.

Discussion

Here we report the association of the self-administration of oral CLO with a lack of significant PLD-associated PPE. This study is limited by its retrospective analysis, non-blinded nature and lack of a placebo-control group. However, even in this limited, exploratory analysis, the concurrent administration of CLO with PLD chemotherapy is impressive considering that with similar PLD dosages and scheduling in prior studies, a 21% incidence of PPE has been observed, including an 8% incidence of severe PPE [9].

Without knowing the mechanistic basis for the development of PLD-induced PPE, we can only speculate as to the exact mechanism by which CLO may mitigate it. One theory for the etiology of PPE involves extravasation

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Table 1. — *Hand-foot skin reaction grades*.*

Grade	Description
1	Minimal skin changes or dermatitis (e.g., erythema) without pain.
2	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function.
3	Ulcerative dermatitis or skin changes with pain interfering with function.

*According to NCI Common Terminology Criteria for Adverse Events (v 3.0).

of PLD from the deeper capillaries of the hands and feet. CLO may decrease this leakage. Jensen *et al.* reported that dietary supplementation with CLO lowered the transcapillary escape rate of albumin in their study of diabetic patients [10]. The mechanism by which CLO normalizes the increased blood vessel permeability in diabetic patients may also play a role in the extravasation of PLD in cancer patients.

Another proposed mechanism for the development of PPE entails a local inflammatory reaction at the site of drug extravasation and accumulation in the stratum corneum. The active ingredients in fish oil include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DME) which are both omega-3-fatty acids. Consumption of EPA has been shown to decrease the production of inflammatory cytokines [11-13]. The decreased production of pro-inflammatory mediators by EPA in CLO may result in a decreased local inflammatory response and account for the lack of severe PPE seen in patients taking CLO supplementation while receiving PLD in our study. An inflammatory model is further corroborated by Drake *et al.'s* study demonstrating the attenuation of PLD-induced PPE with oral dexamethasone which may act to decrease the inflammation cascade [14].

PLD has proven activity in the recurrent ovarian cancer setting. Therapy which may mitigate PLD toxicity thus allowing for prolonged PLD treatment should be investigated. A common dose-limiting toxicity of PLD is PPE. Our finding of a lack of severe PLD-associated PPE with the concurrent use of CLO warrants further evaluation in a prospective, randomized trial, and further attempts are needed to elucidate the mechanism by which CLO may exert its effects.

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Address reprint requests to:
S. LELE, M.D.
Chair, Division of Gynecologic Oncology
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263 (USA)
e-mail: shashi.lele@roswellpark.org