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ORIGINAL ARTICLE

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Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia

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Abstract *Purpose*: Chemotherapeutic regimens that utilize fluorouracil, cytarabine, and doxorubicin have been shown to cause a dermatologic syndrome known as hand-foot syndrome, or palmar-plantar erythrodysesthesia syndrome (PPES). Pegylated liposomal doxorubicin has proven effective in the treatment of AIDS-related Kaposi's sarcoma, ovarian cancer refractory to platinum and paclitaxel therapies, and metastatic breast cancer. In a study of the treatment of refractory epithelial cell ovarian cancers with lipozomal doxorubicin utilizing intravenous doses of 50 mg/m^2 every 3 weeks, grade 3 PPES was observed in 29% of patients (10/35) and required dose reductions and/or dose delay after a median of three therapy cycles. *Methods*: Current methods to prevent pegylated liposomal doxorubicin-induced PPES include dose reduction, lengthening of the drug administration interval and ultimately, drug withdrawal. Topical 99% dimethylsulfoxide (DMSO) also has shown strong activity in treating tissue extravasation reactions during intravenous administration of doxorubicin. *Results*: Two patients undergoing chemotherapy with pegylated liposomal doxorubicin, 50 mg/m^2 every 4 weeks, developed grade 3 PPE after three cycles. Their PPES resolved over a period of 1 to 3 weeks while receiving topical 99% DMSO four times daily for 14 days. *Conclusions*: While these results are promising, patients must be treated in a prospective study of this topical DMSO formulation to definitively document its therapeutic efficacy.

Key words Chemotherapy · Palmar-plantar dysesthesia · Dimethylsulfoxide

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Introduction

Chemotherapeutic regimens that utilize fluorouracil, cytarabine, and doxorubicin have been shown to cause a dermatologic syndrome known as hand-foot syndrome, or palmar-plantar erythrodysesthesia syndrome (PPES) [3, 4, 7, 14, 22]. PPES initially starts with dysesthesia in the hands and feet, followed by edema and erythema, and ultimately, fissuring and ulceration involving the fingers, toes, palms and plantar aspects of the feet. As the syndrome progresses, the patient may experience extreme pain when grasping objects or walking [4, 14, 22]. Histologically the condition is marked by hyperkeratosis associated with an inflammatory cell infiltrate and an increase in vascularity of the dermis [3, 7].

Doxorubicin, an anthracycline, is commonly administered for a wide range of solid tumors such as sarcomas, adenocarcinomas, and hematologic malignancies [2]. Acute dose-limiting toxicities include neutropenia and stomatitis; however, the major dose-limiting toxicity is myocardial damage and resultant congestive heart failure usually seen at doses of 360 mg/m^2 or greater [13, 23]. Liposomal doxorubicin preparations have been investigated as safer and potentially more active alternatives to the parent compound. Polyethylene glycol (PEG) coating of liposomes greatly alters the pharmacokinetics of doxorubicin with the PEG coating reducing the ability of the reticuloendothelial system to eliminate the liposomal materials from the body [6, 19,

21]. Major differences in doxorubicin clearance and distribution along with significant increases in drug concentrations in tumors have been observed as a result of pegylated liposomal encapsulation [6, 17, 19].

Pegylated liposomal doxorubicin has proven effective in the treatment of AIDS-related Kaposi's sarcoma [9, 17, 20], ovarian cancer refractory to platinum and paclitaxel therapies [16], and metastatic breast cancer [21]. In the treatment of refractory epithelial cell ovarian cancers, Muggia et al. [16] utilized intravenous doses of 50 mg/m^2 every 3 weeks. When grade 3 or 4 PPES toxicity was encountered, the dose was reduced to 40 mg/m^2. If grade 1 or 2 toxicity persisted beyond a 3-week period, the administration interval was lengthened to 4 weeks. Grade 3 PPES was observed in 29% of patients (10/35) and required dose reductions and/or dose delay after a median of three therapy cycles.

Current methods to prevent pegylated liposomal doxorubicin-induced PPES include dose reduction, lengthening of the drug administration interval and ultimately, drug withdrawal. However, alteration in drug dose and schedule can compromise the efficacy of a particular treatment regimen, and contribute to suboptimal cancer treatment [5, 8].

Pyridoxine therapy has been utilized to alleviate the onset of PPES during treatment with 5-FU infusions for metastatic colon cancer [4]. The addition of pyridoxine to the combination of altretamine plus cisplatin in stage II–IV epithelial ovarian cancer patients resulted in a significant reduction in response duration [24]. Currently, pyridoxine has been suggested for the management of pegylated liposomal doxorubicin-induced PPES in some phase II trials. The efficacy of pyridoxine in this setting is thus far undocumented.

Topical 99% DMSO also shows strong activity in treating tissue extravasation reactions during intravenous administration of doxorubicin [1, 18]. In a clinical study by Olver et al. [18], 20 consecutive patients were treated with topical 99% DMSO for anthracycline soft tissue extravasation. At 3 months after DMSO treatment, 38% of the patients had no sign of residual damage and in 63% of the patients, only a pigmented, indurated skin lesion remained, without any sign of ulceration. Since no patients progressed to ulceration, the investigators documented a true ulceration rate of 0–17% (95% confidence interval) compared to the 30% progression rate to ulceration observed by Larson [10] when only ice was applied to the extravasation site. More recently, Bertelli et al. [1] have reported complete recovery from doxorubicin extravasation injury in 11 of 11 patients treated three times daily with 99% topical DMSO.

Because of the reported success of 99% topical DMSO in the management of doxorubicin-induced extravasation injury, we initiated an evaluation of this therapy in patients who developed PPES during pegylated liposomal doxorubicin therapy. Discussed below are case reports of the first two patients treated with topical DMSO for PPES caused by pegylated liposomal doxorubicin.

Case reports

Patient number one

A 47-year-old Mexican female with metastatic leiomyosarcoma to the lung was undergoing treatment at the Arizona Cancer Center with pegylated liposomal doxorubicin at 50 mg/m^2 infused over 1 h every 4 weeks. The patient subsequently developed grade 1 PPES with swelling and light discoloration of hands and feet (without evidence of desquamation) prior to administration of the third course of chemotherapy. Despite the use of pyridoxine, 50 mg three times daily, during the 4 weeks following her third treatment cycle, the PPES increased in severity to grade 3 with swelling, erythema, pain and mild desquamation on her hands, as well as blisters on the dorsal aspects of the toes and the left anterior aspect of the wrist. She was seen in the Arizona Cancer Center, at the time of the scheduled fourth treatment, and was instructed to apply 99% DMSO (Burdick & Jackson Division, Baxter Healthcare, Muskegon, Mich.; HPLC-Grade) four times daily to the affected areas, delaying her fourth treatment cycle for 1 week. One week later, the patient was found to be without ulcers or blisters; however, mild skin desquamation remained on her hands and fingers. Pegylated liposomal doxorubicin therapy was continued at 50 mg/m^2 every 4 weeks for two additional 4-week cycles. The signs and symptoms of PPES completely resolved by the time of the fifth course of pegylated liposomal doxorubicin while continuing topical 99% DMSO treatment.

Patient number two

A 66-year old white male with a history of metastatic melanoma (lymph node, skin and lung metastases) received the first cycle of pegylated liposomal doxorubicin, 50 mg/m^2 every 4 weeks plus pyridoxine 50 mg orally three times daily. A second cycle was administered without incident. At the time of the third cycle of chemotherapy, the patient reported a rash, lasting approximately 1 week, on his back, arms and groin, associated with erythema and mild pruritus without desquamation (i.e. grade 1 skin toxicity). When he returned to the Arizona Cancer Center for his fourth therapy cycle, he had a severe rash on his buttocks, hands and feet and was unable to walk, because of grade 3 PPES, with skin edema, erythema, blistering and desquamation on his soles. Pegylated liposomal doxorubicin therapy was held, pending resolution of the severe PPES, and the patient was instructed to apply topical 99% DMSO four times daily to his palms and soles. At his next clinic visit 9 days later, there was complete resolution of sole edema allowing him to walk and skin erythema and desquamation was improved to grade 1–2 in severity. Although pegylated liposomal doxorubicin therapy was not re-administered, at the patient's request, due to fatigue, topical DMSO therapy was continued. Three weeks later, there was complete resolution of the PPES.

Discussion

Pegylated liposomal doxorubicin has been approved for the treatment of Kaposi's sarcoma [9, 17, 20, 21], and more recently has shown considerable clinical activity in patients with advanced ovarian cancer [16]. The optimal dose and schedule for this new agent are limited by a variable incidence of moderate to severe PPES. Pegylated liposomal doxorubicin doses of 50 mg/m^2 every 4 weeks appear active and extremely well tolerated except for the development of severe PPES in up to one-third of patients [16, 21]. As described by Gordon et al. [7], healing of deep ulcerations on dorsal and plantar surfaces of the feet requires drug discontinuation for ≥5 weeks.

Topical DMSO has been used successfully to treat serious doxorubicin skin extravasations [1, 18]. In general the 99% formulation has been used four times daily for up to 14 days to reduce doxorubicin soft tissue damage. We investigated the use of 99% DMSO in the management of pegylated liposomal doxorubicin-induced PPES, because this syndrome likely results from extravasation of small amounts of doxorubicin from the liposomes which lodge and rupture in microcapillaries (with standing and grasping pressure), releasing doxorubicin into the subcutaneous tissue of the palms and soles. DMSO may transport this free doxorubicin into the systemic circulation and/or act as an antioxidant, thereby preventing doxorubicin's toxic effects on the local soft tissues.

The incidence of severe PPES, as a result of pegylated liposomal doxorubicin therapy has been reported to be between 3.4% and 34%, depending on drug dose and schedule [9, 16, 17, 20, 21]. While PPES also is noted to occur with prolonged administrations of other chemotherapeutic regimens (i.e. 5-FU, and cytarabine), no evidence exists that these drugs have a common mechanism for causing this syndrome [3, 4, 7, 11, 12, 14, 15, 22].

The positive results of topical 99% DMSO applied to the palms and soles in the two patients who developed grade 3 PPES while on pegylated liposomal doxorubicin are promising. Obviously, patients must be treated in a prospective study of this topical DMSO formulation to definitively document therapeutic efficacy.

While other studies have suggested the efficacy of pyridoxine in the resolution of PPES in patients treated with 5-FU [4], no protection was evident in these two patients who developed PPES while taking prophylactic pyridoxine therapy. In fact, both patients developed grade 3 PPES. Furthermore, at least one study [24] has documented a pyridoxine-associated reduction of chemotherapy-induced objective response.

In conclusion, PPES is a frequent, painful and debilitating toxic side effect seen with pegylated liposomal doxorubicin and with prolonged infusions of other common chemotherapeutic agents. Resolution of the syndrome without dose reduction or schedule interruption may be possible with 99% DMSO applied topically to PPES-affected areas in patients undergoing pegylated liposomal doxorubicin treatment. The use of DMSO in the treatment of PPES caused by pegylated liposomal doxorubicin, as well as other chemotherapeutic agents, such as 5-FU, should be considered for further investigation.

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