A Safety Review of Pegylated Liposomal Doxorubicin in the Treatment of Various Malignancies

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By David S. Alberts, MD [2]

Many of the more commonly observed adverse effects of standard doxorubicin (Adriamycin) are lessened by pegylated liposomal delivery (Doxil). The slow release of doxorubicin into normal tissue cells via this form of liposomal delivery ameliorates its potential for severe alopecia, nausea and vomiting, cardiotoxicity, and myelosuppressive toxicity. Infusion-related acute reactions are managed by slowing infusion rates and thorough dilution and mixing of the infused drug. Vesicant properties normally seen with doxorubicin are absent. Palmar-plantar erythrodysesthesia can be reduced by decreasing the dose or increasing the dosing interval. Many of these side effects are developing a predictable profile and are manageable. Because of its overall reduced toxicity profile, pegylated liposomal doxorubicin may be well-suited for use in combination chemotherapeutic regimens. [ONCOLOGY 11(Suppl 11):54-62, 1997]

Introduction

With any new chemotherapy agent, the potential enhancement of efficacy must be balanced against its safety profile. This review will examine the safety profile of a new investigational agent, pegylated liposomal doxorubicin (PEG-LD) (Doxil),[1-3] based on information available in the medical literature, interim clinical trial data of PEG-LD in patients with AIDS-related Kaposi's sarcoma (AIDS-KS), patients with solid tumors (COSTART classification),[4] and our own experience with its use at the Arizona Cancer Center. The interim data noted for the solid tumor database uses the Cox Proportional Hazard Model, which categorizes the incidence of side effects based on initial dose levels (10 to 80 mg/m²). The covariates considered were age, gender, and mean dose per cycle at the first incident of toxicity. This method helps to determine potential for toxicity trends based on starting dose intensity and schedule.

Three protocols are currently active: Two phase II studies of PEG-LD in the treatment of prostate and refractory ovarian cancer, and a phase I study using a combination of paclitaxel and PEG-LD in the treatment of breast and gynecological cancers. The potential adverse effects that have been noted with the use of traditional doxorubicin (Adriamycin), and logically warrant investigation with the pegylated liposomal formulation, are gastrointestinal toxicity, infusion-related reactions, injection site reactions, cardiotoxicity, hematologic toxicity, including myelosuppression, and skin toxicities, including alopecia and palmar-plantar erythrodysesthesia (also called [hand-foot syndrome]). Interim safety data based on clinical trials and methods to reduce potential morbidity will be reviewed.

Gastrointestinal Toxicity

The types of gastrointestinal disturbances noted with PEG-LD administration to patients with AIDS-KS are listed in Table 1.[5] Nausea and vomiting have been observed in approximately 17% and 8% of patients, respectively. Less than 5% of these patients have experienced nausea without vomiting beginning on the second or third day after an infusion. This delayed onset of nausea may relate to the prolonged plasma half-life of PEG-LD[6] and coincide with the slow release of doxorubicin from the liposomes into the circulation.

In a randomized, parallel, multicenter trial conducted by Northfelt and colleagues comparing PEG-LD with Adriamycin, bleomycin (Blenoxane), and vincristine (Oncovin) (ABV) in 258 patients with advanced AIDS-KS, the incidence of nausea and/or vomiting in the PEG-LD arm (N = 133) was 35% compared with 58% in the ABV arm (N = 125) (P < .001).[7]

When 308 patients with solid tumors were treated with PEG-LD, 11 (3.6%) experienced World Health Organization (WHO) grade 3-4 nausea and vomiting (Table 2). All events occurred during either the first or second cycle, and most patients had received an initial dose of 50 mg/m².[4] In a phase II trial
of PEG-LD in patients with refractory ovarian cancer, 3 of 35 patients experienced mild nausea and vomiting; no severe cases were reported.[8]

Diarrhea was reported in 8% of the 705 patients with AIDS-KS who received PEG-LD. However, it is difficult to determine whether the diarrhea was due to underlying disease, other concomitant medications, or a direct effect of the agent.[5] In our own experience and that of others, diarrhea does not appear to be a significant problem when PEG-LD is used to treat patients with solid tumors.[4]

Oral candidiasis was reported in 5.5% of patients with AIDS-KS who received PEG-LD. This incidence is higher than that observed when PEG-LD was used in patients with solid tumors and, likewise, probably represents a manifestation of an underlying disease process.[5]

Stomatitis appears to be the most important gastrointestinal toxicity, and has been dose limiting in phase I trials of PEG-LD.[9] As noted in Table 2, 19 of 308 patients with solid tumors experienced grade 3-4 stomatitis. This included 16 of the 299 patients (5%) treated at initial dose levels of less than or equal to 60 mg/m² and 3 of the 9 patients (33%) treated at PEG-LD levels greater than 60 mg/m². Stomatitis was most commonly seen after cycles 1 or 2. Although fewer patients were treated at higher dose ranges, it appears that the higher the mean dose of PEG-LD per cycle, the more likely a patient will experience stomatitis.[4] Indeed, the mean dose per cycle significantly affects the time to first incident of stomatitis (P = .0001).[4]

Table 3 lists dose schedules used by several investigators and the corresponding number of courses without dose reduction. When PEG-LD was dosed up to 40 mg/m², full doses of the drug were maintained with a dose intensity of about 13.4 mg/m² per week.[8] Dosing intervals may be increased, if necessary, for patients to tolerate therapy. Table 4 shows currently recommended dosing adjustments for stomatitis.

### Infusion-Related Reactions

Patients receiving intravenous infusions of PEG-LD may complain of the sudden onset of one or more of the following: flushing, facial swelling, headache, back pain, chills, light-headedness (associated with mild hypotension), tightness in the chest and throat, and shortness of breath.

This reaction was first observed during phase I studies when PEG-LD was given by "piggyback" administration (ie, drug was injected into an existing intravenous line) over a rapid time period. Further experience showed that decreasing the rate of delivery of liposomal particles into the bloodstream reduced this toxicity. Infusion-related reactions may occur more frequently when the drug is delivered by a centrally placed intravenous line, due to the faster drug passage into the circulation. Similar instances of these types of reactions have been reported with the administration of other intravenously delivered colloidal imaging agents. This constellation of symptoms and signs also occurs with the administration of placebo liposomes.

In patients with AIDS-KS, PEG-LD infusion-related reactions most likely occur with the first infusion, and if not present initially, tend not to occur with subsequent doses. These reactions occur infrequently: In one large study they were observed in only 48 of 705 patients (6.8%) and only during the first cycle of therapy.[5] Patients who experience infusion reactions are often described as appearing "lobster red," or present with widespread skin coloration "like an extreme sunburn." The flushing is nonpruritic, and although it may be alarming to patients, it generally disappears within a few minutes. The same phenomenon has been observed when patients were given the drug diluted in normal saline rather than dextrose. Even flushing out the intravenous infusion lines with saline may precipitate the episode. Rechallenging the patient with the same dose usually does not result in a recurrence of the phenomenon, and its presence does not require discontinuation of therapy.[3,5] The reaction has been referred to as a "pseudo-allergic" reaction because it improves with rechallenge.[5] However, although it looks very much like a histamine reaction, it is apparently not related to histamine release.

Infusion-related reactions with pegylated liposomal doxorubicin can generally be avoided by decreasing the infusion rate, and by administering the first 25% of the dose over a 1-hour period, and the remainder over the next 1-1/2 hours. All subsequent infusions can deliver the total dose over a period of 1 hour.[5] Diphenhydramine and topical steroids are reported to provide relief for local infusion-related reactions.[4] In addition, the drug should be prediluted in dextrose to minimize the chances of poor admixture and "streaming" into the infusion lines in a more concentrated form.

### Injection Site Reactions

Extravasation of doxorubicin can cause local tissue necrosis which in some cases is severe enough to
require surgical excision and skin grafting. PEG-LD has been shown to lack vesicant properties, and has been labeled an irritant. In patients with AIDS-KS, only slight edema and erythema with no long-term sequelae from extravasation of PEG-LD was observed.[10]

**Cardiotoxicity**

Cardiotoxicity is a cumulative, dose-limiting toxicity of doxorubicin. The classic study of its dose-response effects by von Hoff et al.[11] demonstrated that 5% of patients who receive a cumulative doxorubicin dose of 450 mg/m\(^2\) (independent of dosing schedule) experience congestive heart failure. At a cumulative dose level of 600 mg/m\(^2\), on an every third-week dosing schedule, the incidence of heart failure reaches 20% to 25%.[11] In another study of 101 adult patients with soft-tissue sarcomas who received at least 430 mg/m\(^2\) doxorubicin, 14% developed congestive heart failure. Additionally, 52% of the 61 asymptomatic patients had cardiac abnormalities detected by radionuclide ventriculograms.[12] The mechanism of this toxicity is well known, and is dependent on the formation of oxygen-free radicals which cause lipid peroxidation of myocardial cell membranes, cardiomyopathy, and, finally, heart failure.

In contrast, the pharmacokinetics and distribution qualities of PEG-LD appear to reduce the incidence of cardiotoxicity dramatically, even at cumulative doses over 550 mg/m\(^2\).[9] Table 5 shows the cardiac function of patients before and after treatment with 550 mg/m\(^2\) or more of PEG-LD.[9] In this phase I study, left ventricular ejection fractions were essentially unchanged despite high cumulative doses of doxorubicin.

Endomyocardial biopsies were performed on 10 patients with AIDS-KS who had received cumulative doses of PEG-LD greater than or equal to 400 mg/m\(^2\) (median cumulative dose: 559.5 mg/m\(^2\)). Samples were assessed for cardiotoxicity using the Billingham pathology scale.[13] (The Billingham score of 0.5 has recently been added to reflect the considerations in heart transplantation, and represents only nonspecific changes. Therefore, a score of 0.5 signifies that there is no evidence of any anthracycline-specific changes). The results of the blinded readings were matched with prior results from 10 control patients who had been treated with doxorubicin at similar cumulative doses (doxorubicin median cumulative dose: 553.5 mg/m\(^2\)).[4] As shown in Table 6, the mean biopsy score was 0.5 for patients treated with PEG-LD and 2.1 for those treated with doxorubicin. These scores were statistically different (P < .001) supporting the observation that patients who received PEG-LD had no or only minimal cardiotoxicity when compared with the control patients.

In a phase II trial of PEG-LD in refractory ovarian cancer patients, multiple-gated acquisition (MUGA) scans were scheduled after cumulative doses of 300 mg/m\(^2\) and every 100 mg/m\(^2\), thereafter. Nine of 35 patients received cumulative doses greater than 550 mg/m\(^2\) (range: 550 - 810 mg/m\(^2\)). None of these patients showed significant decreases in ejection fraction.[8]

**Hematologic Toxicity**

The majority of data on PEG-LD-induced myelosuppression is from clinical studies of patients with AIDS-KS. Leukopenia is the most common hematologic toxicity in this group. In a phase III trial, 258 patients with AIDS-KS were randomized to receive either PEG-LD (20 mg/m\(^2\) every 2 weeks) or ABV (20 mg/m\(^2\) Adriamycin plus 10 mg/m\(^2\) bleomycin plus 1 mg vincristine every 22 weeks to a maximum of six cycles).[7] The incidence of leukopenia was similar on both study arms (42% in the PEG-LD arm and 45% in the ABV arm). In patients taking PEG-LD, myelosuppression was manageable with growth factor support, and few patients discontinued therapy due to neutropenia. Doxorubicin also has been shown to be myelosuppressive in this patient group.[7,14]

In two open, complementary phase I studies of PEG-LD, a total of 56 patients with solid cancers receiving 281 courses of PEG-LD were accrued and evaluated for toxicity. Myelosuppression was not a major problem at the dose levels tested.[8] Initial doses ranged from 20 to 80 mg/m\(^2\) every 3 weeks, and patients progressed to the next level if no or only mild toxicities were observed. Table 7 lists the median nadir counts for both white blood cells and platelets. Median white blood cell nadir counts were well above 2,000 µL and platelet nadir counts were well above 100,000/µL. Granulocytopenic fever was documented in one patient receiving PEG-LD at 80 mg/m\(^2\). There was no indication of cumulative myelosuppression, and treatment-related anemia was generally mild. PEG-LD appears to be less myelotoxic than doxorubicin, but further study is needed in solid tumor patients. Current management of hematologic toxicities is provided in Table 8.

**Skin Toxicities**
Standard doxorubicin is associated with marked alopecia. However, PEG-LD typically causes only minimal alopecia. In a combined database of 705 patients with AIDS-KS who participated in open and controlled studies of PEG-LD, the overall incidence of alopecia was 8.9% (Table 2). In a randomized study of PEG-LD (20 mg/m² every 2 weeks) vs ABV, alopecia was significantly less frequent (11% vs 42%, respectively). In a similar study of PEG-LD (20 mg/m² every 3 weeks) vs bleomycin and vincristine (BV), the incidence of alopecia was 3.3% in the PEG-LD arm and 8.3% in the BV arm. The difference in the incidence of alopecia in these two randomized studies probably relates to the different dosing schedules of PEG-LD.

A dose-limiting adverse effect of PEG-LD therapy is palmar-plantar erythrodysesthesia or hand-foot syndrome. Although, in most cases, the reaction is mild and resolves in one to two weeks, it can be severe and debilitating and require discontinuation of treatment. Symptoms include symmetrical redness of the skin at pressure points, and, less frequently, swelling of the hands and feet. Loss of skin can occur with the use of high doses. The mechanism of this toxicity is unknown. One theory suggests that pressure point distribution, most notably on the hands and soles of the feet, but also evident in other pressure-sensitive areas, is the result of small capillary breakage and localized extravasation of doxorubicin into adjacent subcutaneous tissue. However, PEG-LD is considered an irritant, not a vesicant and, as noted in Table 9, infusion-related extravasations have resulted in localized irritation only.

Alternatively, it has been suggested that liposomes may extravasate in the skin through postcapillary venules, which are in close proximity to the keratinocytes. They are lodged near the blood vessel wall and slowly release their contents over a long period of time. The keratinocytes are exposed and damaged in what is a nonspecific inflammatory response. In phase I studies, palmar-plantar erythrodysesthesia occurred in a substantial number of patients receiving PEG-LD at starting doses of 50 mg/m² or more (Table 10). However, in a multicenter phase II trial of patients with histologically confirmed metastatic breast cancer, the incidence of palmar-plantar erythrodysesthesia was markedly decreased at a PEG-LD dose of 45 mg/m² every 4 weeks (Table 11). In fact, at this dose level, no patients developed grade 4 and less than 16% of patients developed grade 3 palmar-plantar erythrodysesthesia. However, the investigators had gained experience with managing palmar-plantar erythrodysesthesia, and they often stopped treatment at the first signs of grade 1 or 2 toxicity, rather than allowing grade 3-4 toxicity to develop. This decreased incidence of palmar-plantar erythrodysesthesia also has been observed in other ongoing clinical trials which have utilized a dose level of PEG-LD less than 50 mg/m².

Interim safety data support the relationship of dose and frequency to incidence and severity of palmar-plantar erythrodysesthesia (Table 2). Using the Cox Proportional Hazard Model, 44 of 308 (14%) patients in solid tumor trials experienced grade 3-4 palmar-plantar erythrodysesthesia. Further subgroup analysis of these patients based on starting dose revealed that 7 of 119 patients (6%) who received an initial dose of less than 50 mg/m² experienced grade 3-4 palmar-plantar erythrodysesthesia. At starting dose of 50 to 60 mg/m², 35 of 180 (19%) patients experienced grade 3-4 palmar-plantar erythrodysesthesia. Additionally, at this dose level, the time interval between two consecutive PEG-LD administrations was significantly correlated with the time to first incident of palmar-plantar erythrodysesthesia (P = .0001). Only nine patients have received doses greater than 60 mg/m² and two (22%) of these patients experienced grade 3-4 palmar-plantar erythrodysesthesia. When grade 3 palmar-plantar erythrodysesthesia was observed, 13 of 32 patients dropped out of the study. The remaining patients were able to continue on study with dose reductions and increases in dosing interval.

This analysis suggests that the increase in palmar-plantar erythrodysesthesia from 6% (at less than 50 mg/m² PEG-LD) to 19% (at 50 to 60 mg/m² PEG-LD) may be due to the increase in dose, and is schedule-dependent. The majority of cases in this analysis appear to occur at either cycle 2 or 3. Further safety studies are in progress to better define the incidence of palmar-plantar erythrodysesthesia and to assist physicians in the prevention and management of this toxicity. Current recommendations for the management of palmar-plantar erythrodysesthesia are provided in Table 2.

Studies in dogs have shown that the incidence and severity of palmar-plantar erythrodysesthesia is directly related to dosing interval (personal communication, Frank Martin, May 20, 1997). Because it takes at least 3 weeks for PEG-LD to be cleared from the skin, an accumulation is likely if dosing is more frequent than every 3 weeks. Ongoing trials are focusing on reduced doses every 3 weeks or increased doses every 6 weeks. Preventing the initial occurrence of palmar-plantar erythrodysesthesia and treating it as soon as it appears is critical. Patients should be encouraged to wear loose-fitting shoes and clothing and to...
avoid strenuous activity which may cause injury to capillaries. Ice packs may be used to induce vasoconstriction and lessen the inflammatory response. Dimethyl sulfoxide (DMSO) is effective in lessening the effects of doxorubicin extravasation in the skin,[18,19] therefore, it may be of benefit if applied at the first signs of inflammation related to administration of PEG-LD. Others have suggested using free radical scavengers, such as amifostine[20,21] or pyridoxine.

**Discussion**

Much of the information on adverse events reported for PEG-LD is based on patients with AIDS-KS enrolled in four open studies and two randomized, controlled studies. However, clinical trials are currently underway to further evaluate the safety and efficacy of PEG-LD in refractory ovarian carcinoma, metastatic breast carcinoma, lymphoma, and other cancers.[4]

Patients with AIDS-KS often have complications associated with HIV/AIDS which may adversely affect the safety profile of PEG-LD. Most patients in the PEG-LD studies were classified as poor risk in terms of tumor burden, immune system, and overall illness. Thus, it is difficult to determine whether adverse events were due to PEG-LD, to concomitant therapy, or to the patients underlying disease(s). Many of these patients received potentially myelotoxic drugs including antiretrovirals, antivirals, and trimethoprim/ sulfamethoxazole for *Pneumocystis carinii* pneumonia (PCP) prophylaxis. Patients also may have received systemic antifungal medications and colony stimulating factors sometime during the course of their therapy. In addition, the majority of study patients received 20 mg/m² PEG-LD every 2 to 3 weeks, whereas, in clinical practice PEG-LD is most commonly dosed at 20 mg/m² every 3 weeks in patients with advanced AIDS-KS.

Leukopenia appears to be the dose-limiting toxicity for PEG-LD in patients with AIDS-KS. Occasional hypersensitivity reactions, stomatitis, and skin eruptions occur but are self-limiting and not life-threatening.

In two multicenter, comparative, randomized, open-labeled clinical trials of PEG-LD vs ABV or BV, less overall toxicity was observed with PEG-LD. Each of these studies also contained self-administered Quality of Life (QOL) Patient Assessments.[4,22] These assessments revealed that patients receiving PEG-LD showed significant improvement in pain, social functioning, mental health, health distress, and cognitive functioning scales. Patients treated with ABV did not improve significantly in any category. Patients treated with BV improved in cognitive functioning, overall quality of life, health transition, and health distress.[4,23]

Myocardial injury leading to congestive heart failure has limited the therapeutic potential of doxorubicin. Due to doxorubicin’s cardiotoxicity, the cumulative total dose of this agent should be limited to either 550 mg/m², or less than 400 mg/m² if the patient has received prior radiotherapy.[24] Because PEG-LD contains doxorubicin, cardiotoxicity is a potential concern. To date, however, only minimal cardiotoxicity has been observed in patients with AIDS-KS or solid tumors enrolled in PEG-LD clinical trials, even in those receiving high cumulative exposures (eg, 560 to 840 mg/m²).[9] Other liposomal anthracyclines also have shown the potential for reduced cardiotoxicity.[25]

These initial studies are encouraging, but an exact relationship between cumulative exposure of PEG-LD to myocardial injury has yet to be determined. Therefore, caution should be taken in patients who have had prior anthracycline therapy or those who have a history of cardiovascular disease; PEG-LD should be administered in these patients if the potential benefit of therapy outweighs the risk. Cardiac function should continue to be monitored with use of liposomal agents until additional data are available.

The dose-limiting toxicity of PEG-LD when administered as a single agent in non-AIDS-KS patients with solid tumors appears to be cutaneous in origin (stomatitis and palmar-plantar erythrodysesthesia). However, these side effects are generally manageable and more prevalent with doses greater than 50 mg/m² every 3 weeks. Most ongoing studies evaluating pegylated liposomal doxorubicin as a single agent in solid tumors use less than or equal to 50 mg/m² every 3 to 4 weeks. When PEG-LD is used as a single agent, severe myelosuppression appears to be minimal. The decrease in drug-induced myelosuppression compared with traditional doxorubicin may relate to pharmacokinetics.[6] PEG-LD initially equilibrates between the central compartment and the bone marrow, where it is sequestered by macrophages. Doxorubicin subsequently is released by the macrophages at a rate that exposes the marrow to relatively low peak plasma concentrations and plasma concentrations × time products. It is somewhat analogous to the pharmacodynamics of a low-dose continuous infusion.

Toxicities associated with the use of PEG-LD in combination with other chemotherapeutic agents are...
unknown. However, because PEG-LD appears to have non-overlapping toxicities with the most common chemotherapeutic agents (mainly palmar-plantar erythrodysesthesia, with reduced severe nausea/vomiting, myelosuppression, alopecia), it should be evaluated in combination with other cytotoxic and immunologic agents. Studies are currently underway to evaluate further the safety and efficacy of PEG-LD in combination with other chemotherapeutic agents. Of potential benefit to patients is the reduced incidence of alopecia, nausea/vomiting, and risk of extravasational injury. This offers a potential quality-of-life benefit to patients, and may result in a reduced requirement for costly supportive antiemetic therapies and nursing care.

Summary

PEG-LD is a promising anthracycline antibiotic that appears to have unique properties compared with standard doxorubicin. The improved safety profile of this agent in patients with AIDS-KS and solid tumors is most likely due to the ability of pegylated liposomes to dramatically alter the pharmacokinetics of doxorubicin, resulting in higher concentrations of PEG-LD to the site of the tumor, where the drug is preferentially released. Initial safety studies indicate that PEG-LD may be well suited for combination therapy with other cytotoxic agents, as well as novel immunologic agents in development for the treatment of earlier stage disease.

References:


