Original Article

Adverse drug reaction profile of pegylated liposomal doxorubicin versus conventional doxorubicin: An observational study

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ABSTRACT

Background: Potential life-threatening cardiac toxicities limit the lifetime dose of doxorubicin. The pegylation of the molecule protects the drug from detection by methoxypolyethylene glycol resulting increase of circulation time. Encapsulation of doxorubicin inside a pegylated liposome alters bioavailability, biodistribution and thus its biological activity significantly. We conducted an intensive monitoring of the adverse drug reactions (ADRs) profile of pegylated liposomal doxorubicin (PLD) in comparison with conventional doxorubicin in a tertiary care cancer center. **Materials and Methods:** ADR data were collected from 30 patients receiving PLD and 30 age-matched controls receiving conventional doxorubicin in this longitudinal observational study. Severity was graded as per US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEs). For the evaluation of acute and chronic toxicities, we adopted the basic scale from CTCAE version 4 of the National Cancer Institute. **Results:** The median disease duration was greater in PLD arm. Totally, 357 ADRs were noted with PLD and 375 with conventional doxorubicin. Of these, 75 (21%, 95% confidence interval [CI] 13.69-28.33%) in the PLD group and 60 (16.26%, 95% CI: 9.74-22.78%) in the conventional doxorubicin group were of grade 3/4 severity. Common events included myelosuppression, nausea, vomiting, anorexia, stomatitis, palmer-planter erythrodysesthesia, alopecia with PLD and myelosuppression, nausea, vomiting, anorexia, stomatitis, alopecia, and cardio-toxicities with conventional doxorubicin. For hematological toxicities, there was no statistical significant difference between two arms. Furthermore, gastrointestinal toxicities (nausea, vomiting, diarrhea, anorexia and stomatitis) were same for both arms. Among the skin toxicities palmar-plantar-erythrodysesthesia grade 2 toxicity was found in 60% patients receiving liposomal doxorubicin ($P = 0.046$). In cardio-toxicities, left ventricular ejection dysfunction found in 60% patients of conventional doxorubicin arm (P - 0.038). **Conclusions:** This observational study suggests that PLD has a better tolerability with less ventricular dysfunction but increased yet manageable palmar-plantar-erythrodysesthesia. This needs confirmation through further interventional study.

Key words: Adverse drug reactions, doxorubicin, observational study, pegylated liposomal

INTRODUCTION

Doxorubicin, an anthracycline is used for both carcinomas and sarcomas. It intercalates into DNA resulting in inhibition of DNA synthesis through DNA-dependent RNA polymerase. Formation of cytotoxic oxygen free radicals results in single- and double-stranded DNA breaks with subsequent inhibition of DNA synthesis and function. The usual dose in combination therapy is 45-60 mg/m^2 every 3 weeks.[1]

With a lifetime dose of 550 mg/m^2, the use of doxorubicin is limited by its cardiac toxicities.[2,3] The other common toxicities include myelosuppression;[1] leukopenia more common than thrombocytopenia or anemia; Cardiac toxicities[2] ranges from arrhythmias, pericarditis, and/or myocarditis which are usually transient and mostly asymptomatic and not dose-related. Chronic form results in a dose-dependent dilated cardiomyopathy associated with congestive heart failure; skin changes include hyperpigmentation of nails, skin rash, urticaria, and

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hypersensitivity to sunlight. Radiation recall skin reaction can occur at prior sites of irradiation.

To overcome this toxicity profile of doxorubicin, development of liposomal nanoparticle technology to deliver the drug directly to the tumors was established. The drug is protected from chemical and enzymatic degradation, with reduced plasma protein binding, and decreased uptake in normal tissues. It penetrates tumor tissue into which doxorubicin is released. Liposomes are microscopic vesicles composed of the phospholipid bilayer that are capable of encapsulating active drugs.[4] The pegylated liposomes of doxorubicin (PLD) are formulated with surface-bound methoxypolyethylene glycol to protect liposomes from detection by the mononuclear phagocytic system increasing blood circulation time altering bioavailability, biodistribution, and thus its biological activity significantly.[5]

We undertook a longitudinal observational study to compare the adverse drug reaction (ADR) profile of PLD vis-a-vis conventional doxorubicin.

MATERIALS AND METHODS

We included females with ovarian cancer and breast cancer, judged to be suitable for doxorubicin or PLD, given as single or combination regimens with different drugs in the study if they had not received doxorubicin earlier. Patients with significant impairment of liver, kidney, heart, or other vital organs and those with a history of substance abuse were excluded. Each patient enrolled in the PLD arm, an age-matched (within ± 5 years) subject fulfilling the selection criteria was enrolled in conventional doxorubicin arm.

Patients of ovarian cancer and breast cancer of all stages were eligible for inclusion in the study with the intention of administrating at least 4 cycles of either of the drugs and maximum of 6 cycles. Patients in the PLD group received either this drug as monotherapy (n = 9), or as combination therapy with carboplatin (AUC 5) intravenously (IV) on day 1 (n = 3), or with cyclophosphamide 500 mg/m^2 IV on day 1 (n = 18). PLD was infused at a dose of 50 mg/m^2 IV over 1 h whereas conventional doxorubicin was administered within 3-10 min to minimize the risk of thrombosis or perivenous extravasations.

All patients underwent baseline echocardiography and an electrocardiogram (ECG), liver function tests, and complete hemogram prior to starting of chemotherapy cycle. Patients with a baseline echocardiography of <50% ejection fraction were not included in the study. All patients underwent complete blood count at 2 weeks postchemotherapy on days 14 or 15 to estimate the nadir followed by repeat blood counts prior to chemotherapy. For cardiac toxicity, ECG was done whenever the patient was symptomatic and prior to each cycle. Echocardiography was repeated when the patient was symptomatic or after 3 cycles and at the end of therapy. Intervention was made whenever if required.

For each patient, the ADR profile was noted through detailed history, clinical examination, and scanning source documents (e.g. bed head tickets and laboratory test reports) and the data noted on predesigned case report forms. For the evaluation of acute and chronic toxicities, we adopted the basic scale from National Cancer Institute Common Terminology Criteria for Adverse Event version 4 (CTCAE 4.0).[6] ADR causality was assessed by the World Health Organization-Uppsala Monitoring Center standardized case causality assessment criteria.[7]

Adverse drug reaction profiles have been summarized as percentages. Baseline demographic and disease profile were compared using the Mann-Whitney U-test for nonparametric numerical data and Fisher's exact test for categorical data. The incidence of individual reactions was compared by Fisher's exact test. The correlation study of drug dose with cardiac toxicity was analyzed by Pearson correlation test.

RESULTS

The PLD arm had six diabetic and three hypertensive subjects, while the conventional doxorubicin arm included three and six such patients, respectively. These co-morbidities were well-controlled, and subjects continued their regular medicines (insulin, oral hypoglycemic, anti-hypertensives) throughout the duration of chemotherapy.

A baseline demographic and disease-related profile (age, sex, weight, number of chemotherapy drugs per cycle, and the number of follow-up visits) was comparable between the two groups, except for a significantly longer ($P < 0.05$) disease duration in PLD group compared to conventional doxorubicin group [Table 1].

Every patient experienced one or more ADRs. A total of 357 reactions was noted with liposomal doxorubicin arm and 375 with conventional doxorubicin arm. The median number of ADRs per patient was 11.5 (interquartile range [IQR] 9) with PLD, versus 12 (IQR 8) with conventional doxorubicin. These differences were not statistically significant.

Myelosuppression, nausea, vomiting, anorexia, stomatitis, palmer-planter erythrodysesthesia, alopecia were most frequently encountered (incidence ≥5%) ADRs with PLD, whereas myelosuppression, nausea, vomiting, anorexia, stomatitis, alopecia, and cardio-toxicities were the most

Table 1: Baseline demographic and disease profile of study subjects

Parameter	Pegylated liposomal doxorubicin (*n*=30)	Conventional doxorubicin (*n*=30)
Age (years) median	46.0	51.4
Weight (kg) mean	54.0	50.5
ECOG performance (%)		
Status 1	60.0	60.0
Status 2	40.0	40.0
Primary disease (%)		
Breast	60.0	60.0
Ovary	40.0	40.0
Number of chemotherapy drugs per patient	5	6
Number of follow-up visits per patient	2.5±1.2	3.0±0
Disease duration (months) range	17-21	16-20*
Dose (mg) per cycle	55±5.0	60±5.0

All values denote median±interquartile range. *P<0.05, P<0.01 for comparison between groups. ECOG: Electrocorticography

Table 2: Spectrum of ADRs of PLD versus conventional doxorubicin

System affected	ADR	PLD (*n*=357) (%)	Conventional doxorubicin (*n*=375) (%)	*P*
Hematological	Anemia			
	All grades	39 (10.9)	54 (14.4)	0.444
	Severe	6	15	
	Neutropenia			
	All grades	33 (9.2)	33 (8.8)	1.000
	Severe	9	9	
	Thrombocytopenia			
	All grades	6 (1.7)	0	0.241
	Severe	0	0	
Gastrointestinal	Nausea			
	All grades	42 (11.8)	48 (12.8)	0.846
	Severe	15	12	
	Vomiting			
	All grades	27 (7.6)	30 (8)	1.000
	Severe	12	24	
	Diarrhea			
	All grades	12 (3.4)	0	0.057
	Severe	6	0	
	Anorexia			
	All grades	27 (7.6)	30 (8)	1.000
	Severe	0	0	
	Stomatitis			
	All grades	45 (12.6)	24 (6.4)	0.127
	Severe	4	0	
Dermatological	Alopecia			
	All grades	45 (12.6)	57 (15.2)	0.846
	Severe	0	0	
	Palmar-plantar erythrodysesthesia			
	All grades	36 (10.1)	9 (2.4)	0.046
	Severe	12	0	
	Dry skin			
	All grades	9 (2.5)	6 (1.6)	0.680
	Severe	0	0	
	Skin rash			
	All grades	9 (2.5)	3 (0.8)	0.364
	Severe	3	0	
Cardiovascular	ECG abnormalities			
	All grades	3 (0.8)	12 (3.2)	0.370
	Severe	0	0	
	Tachyarrhythmia			
	All grades	15 (4.2)	36 (9.6)	0.130
	Severe	0	0	
	Left ventricular ejection dysfunction			
	All grades	0	18 (4.8)	0.038
	Severe		0	

n: The number of ADRs in each arm. Grading is as per US National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). "Severe indicates grade 3 or 4; the *P* value applies to comparison for all severity grades. ADRs: Adverse drug reactions, ECG: Electrocardiogram, PLD: Pegylated liposomal doxorubicin

common ADRs with conventional doxorubicin [Table 2]. Twelve cases of diarrhea (grade 2 or 3) were noted in the liposomal doxorubicin group; no such event was encountered with conventional doxorubicin. For hematological toxicities, there is no statistical significant difference between two arms. Furthermore, gastrointestinal toxicities (nausea, vomiting, diarrhea, constipation, anorexia, and stomatitis) are same for both arms. Among the skin toxicities, palmar-plantar-erythrodysesthesia grade 2 toxicity was found in 60% patients receiving liposomal doxorubicin (P - 0.046). Among the cardio-toxicities, left ventricular ejection dysfunction found in 60% patients of conventional doxorubicin arm (P - 0.038)

A total of 75 events (21%, 95% confidence interval [CI] 13.69-28.33%) in the PLD group and 60 events (16.26%, 95% CI: 9.74-22.78%) in the conventional doxorubicin group were considered "severe" [Table 2].

For the 12 patients who received PLD monotherapy, the ADRs having either "certain" or "probable/likely" association included anemia (grades 2 and 3), nausea (grade 1), vomiting (grade 2), stomatitis (grade 2), palmer-planter erythrodysesthesia (grades 1 and 2), alopecia (grade 1).

DISCUSSION

Doxorubicin is one of the most commonly used anticancer drugs. Its antitumor efficacy is primarily attributed to direct interactions with DNA or DNA topoisomerase. Mechanisms of action are: (a) Inhibits DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand preventing the replication of rapidly-growing cancer cells; (b) inhibits topoiosomerase II enzyme, preventing the relaxing of supercoiled DNA and thus blocking DNA transcription and replication; and (c) creates iron-mediated free oxygen radicals that damage the DNA and cell membranes.[8]

Myelosuppression and cardiotoxicity are major dose-limiting toxicities of doxorubicin. Acute doxorubicin cardiotoxicity is reversible, and clinical signs include tachycardia, hypotension, ECG changes, and arrhythmias. Acute toxicity develops during or within days of infusion, the incidence of which has been significantly reduced by slowing infusion

rates. Chronic cardiotoxicity peaks at 1-3 months, but can occur even years after therapy.

Nanoparticles in the form of liposomes, dendrimers, and buckyballs came in the field of medicine for improvement of therapeutic index. Liposomes are vesicles with a membrane composed of phospholipid and cholesterol bilayer, usually with an aqueous solution at core, have been used for delivering a wide variety of therapeutics and imaging agents, including small-molecule drugs, gene therapies, and antisense oligonucleotides.[9,10] Because of their ability to sequester DNA or drugs that would not normally enter the intercellular compartment the target drugs encased in a liposome can be delivered to cells through diffusion, as well as receptor-mediated events.

Conventional liposomes are removed from circulation by the reticuloendothelial cells within a few minutes to hours, subsequent to the acquisition of opsonins from plasma.[11,12] For this short circulation half-life, the use of conventional liposome has limited clinical applications. PLDs are able to inhibit opsonization of the liposomes by plasma proteins.[13,14] Prolonged circulation of liposomes leads to better therapeutic efficacy of liposomal anthracyclines, related to increased accumulation of drug-loaded liposomes in tumor tissue.[15,16] The usual doses of liposomal doxorubicin doses range from 20 to 60 mg/m^2 every 3 weeks IV. Clinical trials have shown low cardiac toxicity of this drug without any considerable loss of efficacy.[17-19]

Reactions encountered in the conventional doxorubicin arm (mostly in combination with cyclophosphamide or cisplatin or carboplatin) match the known ADR profile of such combinations. Cardio-toxicities were more common with conventional doxorubicin. Nausea, vomiting, anorexia, alopecia were also more common with conventional doxorubicin.

In addition to the small sample size and limited ethnic and geographic coverage, our study had another limitation of being observational pharmaco-vigilance study. Causality assessment was hampered by the fact that most patients were on combination therapy and the toxicities of doxorubicin overlapped with those of the other drugs used to a substantial extent.

CONCLUSIONS

This observational study suggests that PLD has a better tolerance with less ventricular dysfunction but increased yet manageable palmar-plantar-erythrodysesthesia. A larger randomized controlled trial is needed to confirm the trends shown by this observational study.

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