Original Article

Liposomal doxorubicin: a phase II trial

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Abstract. *Background and aim of the work:* In patients with disseminated endometrial carcinoma, doxorubicin is used as a single agent or in combination therapy. We have carried out a phase II clinical trial of liposomal doxorubicin in first-line therapy of women with disseminated endometrial carcinoma. *Methods:* Between September 2001 and May 2003, 22 patients with histologically confirmed disseminated endometrial carcinoma, were enrolled in this study. Eleven patients had been previously treated with radiation, none of them had been treated with chemotherapy. Liposomal doxorubicin (40 mg/m^2) was intravenously administered at 4 week intervals until toxicity or progression. *Results:* The most common adverse events were fatigue, anemia, pain, and dermatologic toxicity (EPP). Eight patients (36%) achieved a tumor regression (Complete response, CR 3; Partial response, PR 5), ten (46%) maintained stable disease, and four (18%) experienced increasing disease. *Conclusion:* Liposomal doxorubicin has a lower cardiologic toxicity than doxorubicin with a similar response rate in patients with disseminated endometrial carcinoma. (www.actabiomedica.it)

Key words: Liposomal doxorubicin, endometrial cancer, toxicity

Introduction

In patients with disseminated endometrial carcinoma, doxorubicin is used as a single agent or in combination therapy (1). This agent is able to bind to DNA and inhibit nucleic acid synthesis causing DNA strand breaks by binding to topoisomerasi II as it cleaves DNA. However, its cardiac toxicity is well known. Liposomal doxorubicin, doxorubicin encapsulated in long-circulating liposomes, should have less cardiac toxicity, but similar response rates compared to standard doxorubicin. Liposomes are microscopic vesicles composed of a phospholipid bilayer, capable of encapsulating active drugs. The liposome formulations incorporating a synthetic polyethylene glycol-derivatized phospholipid, a process often referred to as pegylation, have a pronounced effect on liposome tissue distribution and can produce a large increase in the pharmacological efficacy of encapsulated antitumor drugs. This effect is associated with a more than 5-fold prolongation of liposome circulation time in blood, a marked decrease in uptake by liver and spleen, and an increased accumulation in tumors (2, 3). Based on a previous study of the Gynecologic Oncology Group (1), we carried out a phase II clinical trial of liposomal doxorubicin in first-line therapy of women with disseminated endometrial carcinoma.

Materials and methods

Between September 2001 and May 2003, 22 patients with histologically confirmed disseminated endometrial carcinoma, were enrolled in this study. All cases presented stage III FIGO endometrioid carcinomas and peritoneal sierosa as the site of dissemination. The patients had a median age of 50 years (ranged 40-70). Eleven patients had been previously treated with radiation, none of them had been treated with chemotherapy. All patients provided written informed consent. The main criteria of inclusion are summari-

Table 1. Main criteria of inclusion

Disseminated endometrial carcinoma
No CHT or RT for a previous malignancy
Measurable disease considered incurable following failure of local therapeutic measures (surgery and/or radiation therapy)
Performance status 0-2 (ECOG)
WBC > 3000/μl; granulocytes >1500/μl; platelets > 100000/μl
Serum creatinine <1,5 mg/dl
Total bilirubin < 1,5 x normal; GOT, GPT < 3 x normal
Normal left ventricular ejection fraction

Table 3. Definition of response

CR (complete response)	No evidence of disease for > 12 weeks
PR (partial response)	Reduction of > 50% of each lesion for > 12 weeks
ID (increasing disease)	Increase of > 50 % of any lesion documented within 12 weeks of study entry or the appearance of any new lesion within 12 weeks of study entry
SD (stable disease)	Any condition meeting none of the above criteria

zed in table 1; the adverse events are calculated with "Common Toxicity Criteria" (2.0 version, 23rd March 1998).

Liposomal doxorubicin (40 mg/m^2) was intravenously administered at 4 week intervals until toxicity or progression. Patients, in which no tumor progression or intolerable toxicity was observed, received maximum twenty cycles of the drug.

All patients were premedicated with steroids, antihistamine, and cimetidyne considering that the liposomal part of the molecule is allergenic. Cardioprotective agents were not used. The cardiac function was monitored by cardiac ultrasound. The therapy was continued until left ventricular ejection fraction was in the normal range. Prior to the initial treatment and during the treatment the patients were monitored as reported in table 2.

Laboratory tests (WBC, RBC, HB, PLT, serum creatinine, total bilirubin, SGOT, SGPT, glucose levels, nitrogen levels, iron levels) were performed every week between consecutive cycles during the entire therapy. In patients with diabetes (type 2) or with glicemic intolerance, liposomal doxorubicin was diluted in a sodium-chloride solution (usually, based on the technical characteristics of the drug, liposomal doxorubicin is diluted in a glucose solution at 5%).

Table 2. Tests used to monitor patients

History and physical examination
PS, weight, body surface area
Serum creatinine, azotemia
Total bilirubin, SGOT, SGPT, blood glucose levels
Haemoglobin, WBC with differential count, platelets, iron levels
CT or MRI for tumor assessment

Moreover CT or MRI was performed after the third cycle, in order to evaluate the drug efficacy .

Response was defined as reported in table 3.

Results

Six patients had previously received pelvic radiation, and five patients previously underwent extrapelvic radiation, both for a maximum of 60 Gy. In these patients an increase of dermatologic toxicity (palmar-plantar erythrodysesthesia, or EPP) was observed.

The most common adverse events were fatigue, anemia, pain and, dermatologic toxicity (EPP). We observed that, among these, EPP was the most common adverse event of liposomal doxorubicin treatment, despite a treatment with B6 vitamin complex which began a week before the first chemotherapy cycle was continued until the end of therapy . Three patients had dark complexion associated with stomatitis and four patients showed only palmar-plater dark macule associated with paralgesia (Fig. 1). In this group of patients with important dermatological reactions (grade 4) liposomal doxorubicin (30 mg/m^2) was administered (dose reduction of 25%) every 4 weeks.

Eight patients (36%) achieved tumor regression (CR 3; PR 5), ten (46%) maintained stable disease, and four (18%) experienced increasing disease (Fig. 2).

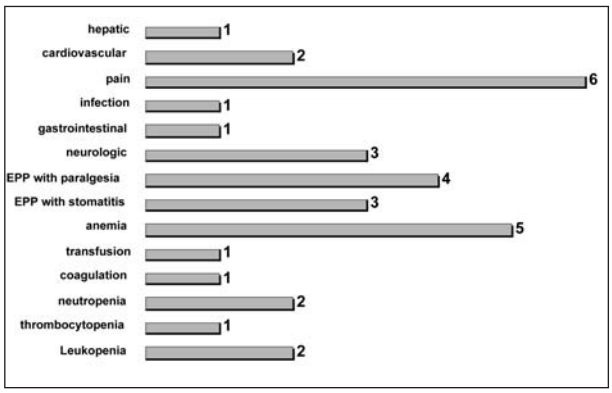

Figure 1. Toxicity of grade 3-4 (CTC v. 2.0-NCIC-CTG)

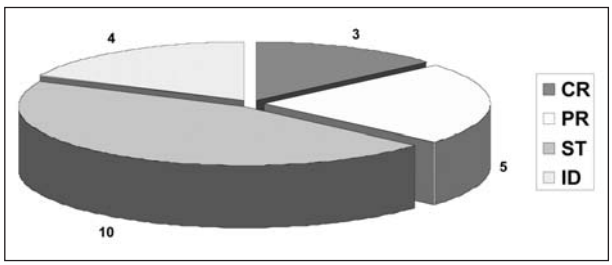

Figure 2. Response rates.

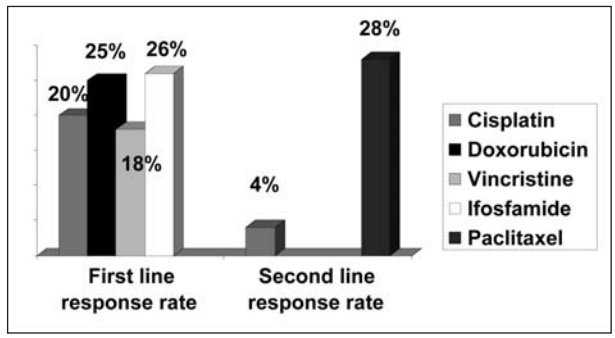

Figure 3. First and second line response rates.

Discussion

We tested a first-line chemotherapy in disseminated endometrial carcinoma with the possibility that liposomal doxorubicin could induce a higher response rate than doxorubicin. In first-line therapy for metastatic breast cancer, liposomal doxorubicin has the same efficacy of doxorubicin, with significantly reduced cardiotoxicity, myelosuppression, vomiting, and alopecia: therefore it was necessary to assess the activity of liposomal doxorubicin alone in disseminated endometrial carcinoma. In the Gynecologic Oncology Group Study, the overall response rate (RR) with liposomal doxorubicin was of 11,5% (1), while previous trials indicated a first-line single agent response rate for doxorubicin of 22-25% (4, 5) . In this study the overall RR was of 36%. The overall response rates of other agents (Paclitaxel, ifosfamide, cisplatin and vincristine) are higher, as summarized in figure 3 (4, 6-10).

It is known that irreversible myocardial toxicity leading to congestive heart failure is possible as the total dosage of doxorubicin approaches 550 mg/m^2 (11, 12). However, liposomal doxorubicin should not have myocardial toxicity. In this study only two patients experienced cardiovascular toxicity. Moreover, the haematological toxicity concerned red blood cells causing serious anaemia (grade 3-4 in 5 patients: all patients used hepoethyn molecules but 1 of them also needed transfusions). These women presented fatigue which is the most common adverse event in this disease. The follow-up of the patients showed a gradual resolution of dermatological adverse events only with the use of B-complex vitamins.

In conclusion, liposomal doxorubicin shows a lower cardiologic toxicity than doxorubicin with a similar response rate in patients with disseminated endometrial carcinoma. For this reason, liposomal doxorubicin is preferable compared to the conventional treatment. However, further studies are needed to increase the drug tolerability especially at a dermatological level.

References

1. Homesley HD, Blessing JA, et al. Phase II trial of liposomal doxorubicin at 40 mg/m^2 every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecologic Oncology* 2005; 98: 294-8.
2. Gabizon A, Barenhonz Y, Bialer M. Prolongation of the circulation time of doxorubicin encapsulated in liposomes containing a polyethylene glycol-derivatized phospholipid:pharmacokinetic studies in rodents and dogs. *Pharm Res* 1993; 10: 703-8.
3. Gabizon A, Pappo O, Goren D, et al. Preclinical studios with doxorubicin encapsulated in polyethylene-glycol coated liposomes. *J Liposome Res* 1993; 3: 517-28.

4. Thigpen JT, Brady MF, Homesley H, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J ClinOncol* 2004; 22: 3902-8.
5. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of recurrent endometrial carcinoma. A Gynecologic Oncology Group Study. *J Clin Oncol* 1994; 12: 1408-14.
6. Thigpen JT, Blessing JA, Homesley H, et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group Study. *Gynecol Oncol* 1989; 33: 68-70.
7. Thigpen JT, Blessing JA, Lagasse LD, et al. Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group Study. *Am J Clin Oncol* 1984; 7: 253-6.
8. Brown GO, Blessing JA, Eddy GL, et al. A phase II trial of vincristine given as a weekly intravenous bolus in advanced or recurrent endometrial carcinoma. *Am J Clin Oncol* 1993; 16: 18-21.
9. Sutton GP, Blessing JA, DeMars LR, et al. A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. *Gynecol Oncol* 1996; 63: 25-7.
10. Lincoln S, Blessing JA, Lee RB, et al. Activity of paclitaxel as a second-line chemotherapy in endometrial carcinoma. *Gynecol Oncol* 2003; 88: 277-81.
11. Muggia FM, Blessing JA, Sorosky J, et al. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2002; 20: 2360-4.
12. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2004; 22: 2159-66.

Accepted: 5th September 2007
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