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Clinical report

Doxil (Caelyx): an exploratory study with pharmacokinetics in patients with hormone-refractory prostate cancer

A Hubert,[1] O Lyass,[1] D Pode[2] and A Gabizon[1]
[1]Sharet Institute of Oncology and [2]Department of Urology, Hadassah Hebrew University Medical Center, 91120 Jerusalem, Israel.

Doxil, a doxorubicin formulation of polyethylene glycol-coated liposomes, has anti-tumor activity against Kaposi's sarcoma and other solid tumors with mild myelosuppression, minimal hair loss and a low risk of cardiotoxicity. Non-liposomal doxorubicin has modest activity in hormone-refractory prostate cancer (HRPC) with considerable toxicity. A pilot study of Doxil was conducted in 15 patients with HRPC. Doxil was administered i.v. using two regimes of equal dose intensity, either 45 mg/m^2 every 3 weeks or 60 mg/m^2 every 4 weeks. Plasma levels of doxorubicin were analyzed in 10 patients. The most common side effect was stomatitis with a higher incidence at the 60 mg/m^2 dose level. In contrast, hand–foot syndrome was more frequent and severe in patients treated with the 3 week schedule of 45 mg/m^2. Three patients responded to treatment (based on objective response in one patient and reduction of PSA level greater than 50% in the other two) and two patients had stable disease, all of them receiving 60 mg/m^2. Pharmacokinetic analysis shows a proportional increase of plasma drug levels with dose and the characteristic long circulation time of Doxil with half-lives in the range of 3 days, somewhat longer than previously reported. In conclusion, Doxil at 60 mg/m^2 every 4 weeks appears to be active against HRPC, but severe mucocutaneous toxicities prevented further investigation of this regime. [© 2000 Lippincott Williams & Wilkins.]

Key words: Cancer, chemotherapy, doxorubicin, human, liposome, prostate.

Introduction

Although the role of cytotoxic chemotherapy in hormone-refractory prostate cancer (HRPC) is controversial,[1,2] it is well established that anthracyclines such as doxorubicin and its congener mitoxantrone have modest activity.[3,4] The latter has been approved in the US and other countries in combination with prednisone based on a recent study which showed 33% PSA response and a significant improvement in quality of life.[5] Doxorubicin is widely used in cancer chemotherapy, but has significant limitations in the setting of HRPC which affects a population with a large subset of elderly patients. This is due mainly to the severe toxicity of doxorubicin including severe myelosuppression and cardiotoxicity.[6] Doxil (also known as Caelyx) is a formulation of polyethylene glycol-coated liposomal doxorubicin approved for the treatment of AIDS-related Kaposi's sarcoma,[7,8] and with promising indications of activity in some types of solid tumors such as ovary and breast carcinomas,[9,10] although, notably, soft tissue sarcomas appear to be quite resistant to standard doses.[11] Doxil has a distinct toxicity profile, which points, on the one hand, to attenuation of myelosuppression, alopecia and probably cardiotoxicity, and, on the other hand, to significant muco-cutaneous toxicities.[12] The need for effective and yet tolerable chemotherapy in HRPC patients led us to explore the toxicity and activity of Doxil in this setting. Based on the results of a phase I study in patients with solid tumors,[12] we chose to investigate two dose schedules (60 mg/m^2 q 4 weeks, and 45 mg/m^2 q 3 weeks) of equal dose intensity (15 mg/m^2/week). In addition, plasma drug levels were measured to analyze and compare the pharmacokinetics of the two dose levels tested.

Patients and methods

All eligible patients had histologically confirmed adenocarcinoma of the prostate with metastatic

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Correspondence to A Gabizon, Oncology Department, Hadassah Medical Center, Kiryat Hadassah, POB 12000, 91120 Jerusalem, Israel.
Tel: (+972) 2 677 6677; Fax: (+972) 2 643 0622
E-mail: alberto@md2.huji.ac.il

disease progressing on hormonal therapy, including castration (LH-RH analogs or orchiectomy), anti-androgens (cyproterone acetate, flutamide) and, in some patients, aminogluthetimide plus hydrocortisone or diethyl-stilbestrol. All patients had evaluable or measurable tumor, Karnofsky performance score $\geqslant$50%, adequate hepatic function (bilirubin <35 μmol/l, transaminases $<3\times$ normal levels), reasonably preserved renal function (creatinine <200 μmol/l) and blood counts (WBC $\geqslant 3000/\mu$l; neutrophil count $\geqslant 1500/\mu$l; hemoglobin $\geqslant 10$ g%; platelet count $\geqslant 75\,000/\mu$l). A baseline cardiac ejection fraction $\geqslant$50% was required. All patients signed witnessed informed consent. The clinical protocol was reviewed and approved by the institutional review board of Hadassah Hebrew University Medical Center.

Pre-treatment evaluation included history and physical examination, complete blood cell count, biochemistry, and CEA and PSA levels. Baseline diagnostic imaging studies included chest radiograph, CT examination of the abdomen and pelvis, and radionuclide bone scan. Patients were treated with Doxil in two different dose schedules with an equal dose intensity, 15 mg/m^2/week, based on the maximum tolerated dose (MTD) established in a phase I study,[12] as part of an exploratory study with pharmacokinetics in HRPC. Schedule I consisted of i.v. Doxil 45 mg/m^2 every 3 weeks. Schedule II consisted of 60 mg/m^2 every 4 weeks. A cohort of 10 patients was randomized to either schedule. Additional cohorts of 10 patients were to be treated at either schedule, depending on treatment tolerability of the first cohort. Because of the severe skin toxicity of schedule I (see Results), only five more patients were accrued and treated with schedule II (60 mg/m^2 every 4 weeks). Toxicity was graded from 1 to 4 using the NCI common toxicity criteria. If grade 3 or 4 toxicity (myelosuppression or stomatitis) occurred the dose of subsequent courses was reduced by 20%. In case of skin toxicity the subsequent dose was delayed until grade was 0 or 1 and in severe cases (Grade 4) the dose was also reduced by 20%. Response was evaluated by monthly PSA level, a well-established surrogate marker of response[13–15] and imaging studies, if measurable parameters present, after each two or three courses for 60 mg/m^2 q 4 weeks and 45 mg/m^2 q 3 weeks, respectively. Cardiac ejection fraction per MUGA scan was rechecked in patients receiving >300 mg/m^2 cumulative dose.

Doxil, a liquid suspension of doxorubicin-loaded, polyethyleneglycol-coated liposomes, was provided by Sequus Pharmaceuticals (Menlo Park, CA) [Doxil is currently a product of ALZA Corp (Mountain View, CA]. Doxil was administered i.v. as previously reported.[12] In this study, there were no acute reactions to infusion reported.

Plasma levels of doxorubicin after Doxil injection were investigated in seven patients receiving 60 mg/m^2 and five patients receiving 45 mg/m^2. Blood was sampled at the end of infusion, and 4, 24 and 72 h, and 7, 14 and 21 days after infusion. Extraction of drug and measurement by HPLC was done as previously described.[16] Measurements were based on total drug in plasma since previous studies have shown that, in the case of Doxil, it is practically equivalent to liposome-associated drug in plasma.[16] Pharmacokinetic data were processed by non-linear least squares analysis using Rstrip software (MicroMath, Salt Lake City, UT).

Results

Table 1 lists the characteristics of 15 patients with metastatic prostate cancer entered into the study. All patients had prior hormone therapy until progression. Two patients had one line of prior chemotherapy. As listed in Table 2, 10 patients received a starting dose of Doxil 60 mg/m^2 every 4 weeks and five patients were given 45 mg/m^2 every 3 weeks. Dose reduction was required in seven of the patients, five in the 60 mg/m^2 group and two in the 45 mg/m^2 group, due to stomatitis (four cases), skin toxicity (two cases) and myelosuppression (one case). Two patients, one from each schedule group, received only one course of Doxil due to rapid deterioration and disease progression.

The major clinical adverse events were stomatitis (grade 3–4 in four of 15 patients) and skin toxicity in

Table 1. Patient characteristics at baseline

No. of patients	15
Median age [years (range)]	68 (59–78)
Median Gleason score	8 (5–10)
Karnofsky performance status (range)	70 (50–90)
Prior prostate radiotherapy/surgery (*N*)	4/1
Prior chemotherapy (*N*)[a]	2
Median PSA [ng/ml (range)][b]	107 (2.2–>1000) ng/ml
Median hemoglobin [g% (range)]	12.4 (9.8–14.8) g%
Sites of disease (*N*): bone only/bone+visceral/ visceral only	11/2/4
Median duration of hormone-dependent metastatic phase [months (range)]	30 (5–60)

[a]Chemotherapy given: cyclophosphamide with 5-fluorouracil in one patient (one course only) and estramustine with vinblastine in another patient.
[b]One patient had a normal PSA and an elevated CEA.

the form of hand–foot syndrome (grade 3–4 in three of 15 patients). Stomatitis was dose dependent with higher incidence (nine of 10 patients with grade 1–4) at dose level 60 mg/m^2 as compared to 45 mg/m^2 (two of five patients with grade 1–2), a difference of borderline significance (Fisher's exact test, p=0.0769; χ^2 test, p=0.039) in this small patient group. In most cases, stomatitis developed 10–15 days after the first course and lasted for about 5–10 days. In contrast, skin toxicity was schedule dependent, appearing only after a minimum of two courses with higher incidence at 45 mg/m^2 every 3 weeks (four of four patients) than at 60 mg/m^2 every 4 weeks (four of nine patients). As seen in Table 2, the target dose intensity was not reached in any of the patients receiving three or more courses, due to frequent dose delays caused by delayed skin toxicity and slow recovery from stomatitis. Myelosupression was mild and did not necessitate dose modification except for one case with disease-related disseminated intravascular coagulation. Moderate hair loss was seen in only one patient at 60 mg/m^2. There was no evidence of clinical cardiac toxicity or significant decrease (>10%) of left ventricle ejection fraction in any patient.

The anti-tumor responses listed in Table 3 consisted of three partial responses, based on a PSA drop of >50% in two patients with no measurable disease and >50% reduction of measurable disease in one patient with retroperitoneal lymphadenopathy and hydronephrosis in whom the response enabled removal of a nephrostomy drain. Two more patients had stable disease as indicated by PSA reduction <50%, symptomatic relief, no new lesion and no significant change in any known lesion. All responses belong to the 60 mg/m^2 q 4 weeks group. The median time to treatment failure was 6 months (range 4–9). The median survival of all patients was 8 months. The median survival of responding patients was 12 months.

Pharmacokinetic analysis (Table 4) shows a small volume of distribution only slightly greater than the plasma volume, and a slow monoexponential clearance with a mean $t_{1/2}$ of the order of 3–3.5 days (about 75–90 h). The changes in mean C_{max} and AUC values

Table 2. Treatment administration and toxicity

Start dose schedule	60 mg/m^2 q 4 weeks	45 mg/m^2 q 3 weeks
Courses per patient, median (range)	5 (1–9)	3 (1–6)
Cumulative dose, mg/m^2 (range)[a]	258 (60–540)	124 (45–240)
Last dose, mg/m^2 (range)[ab]	52 (34–60)	41 (34–45)
Dose intensity, mg/m^2/week (range)[a,b]	13.3 (12.0–14.6)	11.2 (11.3–13.2)
Stomatitis		
grade 1–2	5/10	2/5
grade 3–4	4/10	0/5
Hand–foot syndrome[c]		
grade 1–2	4/9	1/4
grade 3–4	0/9	3/4

[a]Median values.
[b]Patients receiving three or more courses.
[c]Patients receiving two or more courses.

Table 4. Pharmacokinetic parameters in Doxil-treated HRPC patients[a]

	60 mg/m^2 (7)		45 mg/m^2 (5)	
	Median	Mean (CV)[b]	Median	Mean (CV)[b]
C_{max} (mg/l)	21.0	21.6 (24%)	17.5	17.2 (22%)
AUC (mg·h/l)	2359	2813 (35%)	1710	1828 (20%)
$t_{1/2}$ (h)	89.8	90.7 (31%)	70.5	74.8 (23%)
Cl (ml/h)	45	43 (34%)	44	45 (18%)
V_{SS} (l)	5.1	5.3 (25%)	4.9	4.8 (24%)

[a]The plasma concentration–time data were best fitted to a monoexponential equation as: $C_{(t)}=A\cdot e^{-kt}$, where $C_{(t)}$ is the drug concentration at time t, A is the y-intercept and k is the first-order elimination rate constant. C_{max} is plasma concentration immediately after the end of infusion. AUC (area under the concentration*time curve), $t_{1/2}$ (half-life), Cl (clearance) and V_{SS} (volume of distribution at steady state) were calculated as previously reported.[16]
[b]Coefficient of variation.

Table 3. Anti-tumor responses (N=5)

Response	Start dose (mg/mg^2)	Baseline PSA (ng/ml)	Nadir PSA (ng/ml)	Time to disease progression[a] (months)	Survival[a] (months)
Partial	60	82	2.5	5	12
Partial	60	249	97	7	18
Partial	60	32	6.5	6	8
Stable	60	85	85	4	8
Stable	60	127	70	9	20

[a]Months from start of Doxil treatment.

from the 45 to 60 mg/m^2 dose groups were proportional to the relative change in dose given. Other pharmacokinetic parameters were similar when both dose levels were compared, although there was a trend to an increase in $t_{1/2}$ with dose which did not reach statistical significance. Because of the high incidence of stomatitis at 60 mg/m^2, we looked at a correlation between pharmacokinetic parameters (C_{max}, AUC, $t_{1/2}$, Cl) and stomatitis grade among the seven patients tested in this group, and found a significantly positive correlation only with C_{max} (r=0.756, p=0.049). Of note, the patient with the lowest C_{max} at 60 mg/m^2 (15.3 mg/l) tolerated nine courses of Doxil at 60 mg/m^2 with no dose reduction and no stomatitis. In five patients (three at 60 mg/m^2 and two at 45 mg/m^2), blood sampling for Doxil levels and pharmacokinetic analysis was repeated after the third course of Doxil. When the results of the first course were compared to the third course, major intra-individual variation (>50% change) in pharmacokinetic parameters was observed in only one patient with a 2.25-fold acceleration in clearance and a 40% shortening of half-life.

Discussion

In metastatic carcinoma of the prostate, hormonal treatment (androgen deprivation or blockade) will result in disease regression in as many as 85% of the treated patients.[17] However, relapse and hormone-refractory disease eventually develop in nearly all the patients and portend a somber prognosis with median survival of only 6 months in symptomatic patients.[18] There is a need for more effective forms of chemotherapy in this palliative setting. Recent studies showed that prostate cancer is not as unresponsive to chemotherapy as previously believed.[3–5,19–21]

In this pilot study, Doxil was examined in a small group of patients with HRPC. The clinical data indicate that toxicity is affected by the dose-schedule regime. Despite the fact that both treatment schedules tested here had the same initial dose intensity (15 mg/m^2/week), our results suggest a schedule of 60 mg/m^2 every 4 weeks (schedule II) entails a higher incidence of stomatitis, but less severe skin toxicity, than a schedule of 45 mg/m^2 every 3 weeks (schedule I). This schedule dependence of skin toxicity is in agreement with a phase I report on Doxil.[12]

The toxicity profile of Doxil in HRPC patients as seen here appears similar to that seen in other solid tumor patients,[9,10] i.e. predominant mucocutaneous toxicity with mild myelosuppression and minimal hair loss. Altogether, it was found that neither schedule I nor schedule II are tolerable in this patient population with HRPC, due to the high incidence of cutaneous and mucosal toxicities, respectively. However, there is evidence of modest activity of Doxil in HRPC in this small pilot study. The data indicate that the higher dose tested (60 mg/m^2) can induce responses in this relatively chemo-refractory tumor and justifies further studies. Further exploration of Doxil in the treatment of HRPC will require studies designed with lower dose intensities to improve control of mucocutaneous toxicities. In addition, pharmacologic interventions that may attenuate skin toxicity such as pyridoxine, as suggested in a dog study,[23] or mucositis may improve significantly the prospects of Doxil chemotherapy in HRPC and other conditions. Because of the long half-life of Doxil, ice cooling of the oral mucosa to attenuate stomatitis is impractical.

On the positive side, hematological toxicity of Doxil and hairloss are mild. In addition, none of the patients developed cardiac symptoms. A report of Berry *et al.*[24] demonstrates that Doxil, 20 mg/m^2, induced significantly less damage in cardiac biopsies of Kaposi's sarcoma patients, as compared to control patients with comparable cumulative doses of doxorubicin, pointing to a reduced cardiotoxicity of Doxil which awaits to be confirmed in solid tumor patients.

Regarding pharmacokinetics, results are grossly consistent with previous findings,[16,25] indicating that Doxil has an extremely long circulation time with a small volume of distribution. However, it should be noted that the mean $t_{1/2}$ value obtained here (about 75–90 h) is remarkably longer than previously published in solid tumor patients receiving 50 mg/m^2 ($t_{1/2}$ 45–46 h) using an earlier formulation of Doxil[16] and in AIDS-related Kaposi's sarcoma patients receiving 10–20 mg/m^2 ($t_{1/2}$ 50–55 h).[25] In the latter case the difference is accountable for by the lower dose given and the fact that Doxil shows a trend to dose-dependent saturation of clearance at doses above 40 mg/m^2.[26] In the former case, the explanation for the difference relies probably on the relatively lower ammonium sulfate concentration used in that early, frozen-stored, formulation of Doxil, a factor that may slightly decrease stability and increase drug leakage.[27] As seen in Table 4, the difference in dose between the two schedules was clearly reflected in C_{max} and AUC values, pointing to a strong correlation between dose and plasma levels as previously reported.[16,25] The fact that a 25% reduction in dose is sufficient to cause a predictable change in plasma drug levels and severity of stomatitis, and the correlation between C_{max} and stomatitis grade at the dose of 60 mg/m^2 point to a pharmacokinetic–pharmacodynamic relationship for Doxil. This is in agreement with previous findings in

patients with AIDS-related Kaposi's sarcoma[25] and strenghtens the relevance of complementary pharmacokinetic evaluation of Doxil in further clinical studies.

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