Cancer Chemother Pharmacol (1999) 43: 516–519 © Springer-Verlag 1999

SHORT COMMUNICATION

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Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma – drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study

Received: 29 June 1998 / Accepted: 22 October 1998

Abstract *Purpose:* To describe the pharmacokinetics of paclitaxel and to investigate the interaction potential with protease inhibitors (indinavir, ritonavir, saquinavir) and the nonnucleoside reverse transcriptase inhibitor nevirapine, for which strong theoretical indications for clinically relevant drug interactions exist. *Methods:* The 24-h plasma pharmacokinetics of paclitaxel (Taxol, given at 100 mg/m^2 by 3-h intravenous infusion) and concomitantly infused antiretroviral drugs were determined in a human immunodeficiency virus 1 (HIV-1)-infected male patient with refractory Kaposi's sarcoma (KS) during high-activity antiretroviral therapy and after discontinuation of this regimen. The plasma pharmacokinetics of paclitaxel, indinavir, ritonavir, saquinavir, and nevirapine were closely monitored. Since all these drugs are extensively metabolized via the cytochrome P450 enzyme system and are substrates for the multidrug transporter P-glycoprotein, investigation of drug-drug interactions was considered important. *Results:* In this case report study the pharmacokinetics of paclitaxel given concomitantly with various antiretroviral drugs were comparable with those of historical controls who had been treated with single-agent paclitaxel. The pharmacokinetics of indinavir, ritonavir, saquinavir, and nevirapine were also not statistically significantly different from those recorded for historical controls. Paclitaxel was well tolerated and resulted in a significant clinical response in this patient. *Conclusion:* Dose adjustments of paclitaxel, indinavir, ritonavir, saquinavir, or nevirapine are apparently not needed if HIV-1-associated KS is treated with paclitaxel at a dose of 100 mg/m^2 as shown in the present case. It is stressed, however, that controlled studies are necessary to substantiate these preliminary case report findings.

Key words Antiretroviral agents · Kaposi's sarcoma · Paclitaxel · Pharmacokinetics

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Introduction

The most common malignancy complicating human immunodeficiency virus 1 (HIV-1) infection is Kaposi's sarcoma (KS). Evidence is now accumulating from recent studies that KS is caused by a human herpes virus (HHV-8) [1, 20]. KS lesions (red-purple to red-brown) are often observed on the skin and oral mucosa and in the lymph nodes and viscera (predominantly gastrointestinal and pulmonal) of HIV-1-infected individuals. Morphologically, KS shows proliferation of spindle cells mixed with fibroblasts that secrete factors that stimulate the invasiveness of vascular endothelial cells, which makes KS a highly invasive and intensely angiogenic neoplasm [25].

Paclitaxel (Taxol) is a taxane derivative that favors the assembly of microtubuli with altered stability properties. Paclitaxel has been found to be effective in several malignancies, including head and neck and non-small-cell lung cancers, and has been licensed for the treatment

of advanced breast and ovarian cancer. Adverse effects of paclitaxel are neutropenia, peripheral neuropathy, alopecia, nausea, mucositis, myalgia, and hypersensitivity reactions [22]. The unique mechanism of action and antitumor activity of this drug, combined with its profound antiangiogenic activity, provides strong rationales for the use of paclitaxel in HIV-1-associated KS, after KS progresses or if KS-afflicted patients become intolerant to vincristine, bleomycin, or (liposomal) anthracyclines [2, 17]. Paclitaxel has previously demonstrated impressive antitumor activity (overall response rates ranging from 53% to 71%) in patients with HIV-1-associated KS [3, 9, 23, 28].

Four HIV protease inhibitors that have marked effects on viral load and CD_4+ T-cell counts have been licensed. Treatments with these compounds has demonstrated improvement in survival and disease progression in large clinical trials. Saquinavir (Invirase) is well tolerated. Indinavir (Crixivan) is a potent drug that produces few gastrointestinal and neurological adverse effects but is associated with nephrolithiasis and hyperbilirubinemia [12]. Ritonavir (Norvir) was also licensed because of its beneficial antiretroviral effect, but it often causes gastrointestinal symptoms, paresthesias, and elevated levels of hepatic enzymes. In addition, ritonavir is a very potent inhibitor of cytochrome P450 isoenzymes, particularly CYP3A4 and CYP2D6 [4, 12]. Nevirapine (Viramune) is the first representative of a new class of antiretroviral agents and is a potent and selective noncompetitive inhibitor of the viral reverse transcriptase. This drug is a strong inducer of the cytochrome P450 system [21].

Concern exists as to whether paclitaxel should be used in combination with protease inhibitors, since paclitaxel is mainly metabolized by cytochrome P450 enzymes [6, 10, 22]. The concomitant administration of paclitaxel and protease inhibitors may thus theoretically lead to changes in the plasma concentration of paclitaxel and/or protease inhibitors. In addition, all of these compounds are substrates for drug-transporting P-glycoproteins, which may also lead to changes in pharmacokinetics [16]. The clinical significance of these theoretical considerations are not known; pharmacokinetic data about these putative drug-drug interactions are presently lacking. We investigated the pharmacokinetics of paclitaxel and possible drug-drug interactions between paclitaxel and saquinavir, ritonavir, indinavir, and nevirapine in a patient with HIV-1-associated KS.

Patient and methods

Presentation of case

The patient was a 49-year-old male diagnosed with HIV-1 infection in May 1997. The extent of pulmonary KS resulted in dyspnea, and after systemic combination chemotherapy with several courses of Adriamycin, bleomycin, and vindesin and second-line liposomal daunorubicin, KS continued to progress. In December 1997 we started treatment with paclitaxel (Taxol). At that time the patient had been receiving stavudine at 40 mg b.i.d., lamivudine at 150 mg b.i.d., saquinavir at 400 mg b.i.d., and ritonavir at 400 mg b.i.d. since May 1997. Pharmacokinetic sampling was performed with the purpose of evaluating the influence of the antiretroviral agents on paclitaxel pharmacokinetics. At 1 week after this first course, treatment with saquinavir, ritonavir, lamivudine, and stavudine was discontinued because of adverse effects consisting of paresthesias, which had also been present before the start of paclitaxel treatment.

Pharmacokinetic sampling of paclitaxel during the second course was performed. At this time the patient was not undergoing antiretroviral therapy. Immediately thereafter, treatment with nevirapine (200 mg b.i.d.) was started, and during the third paclitaxel course, pharmacokinetic sampling was repeated. No change was made in the antiretroviral therapy during the following two courses of paclitaxel, and we decided not to execute pharmacokinetic sampling. Meanwhile, the patient had developed a skin rash, which was attributed to nevirapine and necessitated its discontinuation. Nevirapine was replaced by ritonavir (100 mg b.i.d.) plus indinavir (1200 mg b.i.d.), and pharmacokinetic sampling was performed after 3 weeks during course 6. Both the hematological and nonhematological toxicities of paclitaxel were mild during the six courses, and the patient has since retained a significant clinical response. Informed consent was obtained from this patient.

Pharmacokinetics studies and analyses

Paclitaxel was given at 100 mg/m^2 as a 3-h continuous intravenous infusion. Standard premedication consisted of dexamethasone (20 mg given orally at 12 and 6 h prior to paclitaxel infusion), clemastine (2 mg given intravenously at 30 min prior to paclitaxel treatment), and ranitidine (50 mg given intravenously at 30 min prior to paclitaxel infusion). Samples for pharmacokinetic analysis were collected by intravenous sampling from the arm contralateral to the one receiving the paclitaxel infusion, and samples were collected in heparinized tubes prior to the start of the paclitaxel infusion; at 1 and 2 h during the infusion; at the end of the 3-h infusion; and at 5, 15, and 30 min as well as 1, 2, 3, 6, 8, 18, and 24 h after the end of the paclitaxel infusion. Plasma was obtained by immediate centrifugation (5 min; 3000 *g*). Paclitaxel was measured by a sensitive high-performance liquid chromatography (HPLC) assay using solid-phase extraction as a sample pretreatment procedure as previously described [14]. The area under the concentration versus time curve ($AUC_{0-\infty}$) was determined using the trapezoidal rule from the concentration-versus-time plots with extrapolation to infinity. The clearance of paclitaxel (CL) was calculated as $CL = dose/AUC$, whereas the volume of distribution at steady state (V_{ss}) was given by:

$$V_{ss} = \frac{D_{iv}.AUMC}{AUC^2} - \frac{D_{iv}.T}{2.AUC},$$

where D_{iv} is the dose, $AUMC$ is the area under the moment curve, and T is the infusion time. On the day of sampling the antiretroviral drugs were taken after an overnight fast before the start of the paclitaxel infusion (except for course 2, where no antiretroviral agent was given). The samples for saquinavir, ritonavir, indinavir, and nevirapine analysis were collected before intake, at 30 min after intake, and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 h after intake. Concentrations in plasma of saquinavir, ritonavir, indinavir, and nevirapine were assayed by validated, sensitive assays as previously described [11, 13, 26, 27]. The pharmacokinetics of saquinavir, ritonavir, indinavir, and nevirapine were determined by noncompartmental methods during the full dosing interval of 12 h.

Results

The pharmacokinetic parameters determined for paclitaxel, saquinavir, ritonavir, and nevirapine are shown

Table 1 Pharmacokinetic parameters determined for paclitaxel, saquinavir, ritonavir, nevirapine, and indinavir (*C1* paclitaxel + saquinavir + ritonavir + lamivudine + stavudine; *C2* paclitaxel without antiretroviral agents; *C3* paclitaxel + nevirapine + zidovudine + lamivudine; *C6* paclitaxel + ritonavir + indinavir + zidovudine + lamivudine; *AUC* area under the plasma concentration versus time curve – extrapolated to infinity for paclitaxel, 0–12 h for saquinavir, ritonavir, indinavir, and nevirapine; C_{max} = peak plasma concentration; *CL* clearance; V_{ss} volume of distribution at steady state; $t_{1/2}$ = terminal half-life; *C* = course)

	AUC (h μmol/1)	C_{max} (μmol/l):	CL ($l/h^{-1}m^{-2}$)	V_{ss}(l)	T > 0.1 μmol/l (h)
Paclitaxel (C1)	4.9	1.5	20.4	174	7.3
Paclitaxel (C2)	6.2	1.2	15.9	159	18.1
Paclitaxel (C3)	5.0	1.2	21.6	106	9.3
Paclitaxel (C6)	5.9	1.4	20.0	88	11.7
Saquinavir (C1)	42.8	5.1			
Ritonavir[a] (C1)	61.9	9.6			
Nevirapine (C3)	263.6	25.9			
Ritonavir[b] (C6)	13.3	1.9			
Indinavir (C6)	87.2	22.3			

[a]400 mg b.i.d.
[b]100 mg b.i.d.

in Table 1. The paclitaxel AUC and C_{max} values were lower in the three courses in which antiretroviral agents were given concomitantly (courses 1, 3 and 6) as compared with the course in which these agents were not used (course 2). Furthermore, the clearance of paclitaxel was markedly attenuated in course 2, whereas the T > 0.1 μmol/l was considerably prolonged. The C_{max} value was slightly decreased and the clearance of paclitaxel was higher in course 3 (nevirapine) as compared with courses 1 and 6 (combinations of ritonavir with either saquinavir or indinavir); the differences, however, were small. The pharmacokinetic parameters recorded for paclitaxel were comparable with those noted for non-HIV-1-infected historical controls [14, 15]. The pharmacokinetic parameters determined for saquinavir, ritonavir, indinavir, and nevirapine also did not differ from the data reported in the literature [12, 19, 21].

Discussion

The major goal of current treatment of KS is palliation of symptoms such as pain and bleeding and reduction of the tumor size to alleviate edema, organ compromise, or cosmesis. At the early stages, local treatment with surgical excision, radiation therapy, laser therapy, cryotherapy, or intralesional therapy or topical treatment with α-interferon can be beneficial. However, in patients with rapidly progressive KS and/or extensive pulmonary involvement, systemic chemotherapy should be considered. Combinations of doxorubicin, bleomycin, and vincristine have been found to be highly effective, although other investigators have recommended liposomal doxorubicin, which has more advantageous pharmacokinetic properties, is well tolerated, and yields higher response rates [5, 8, 18, 24].

In this case report we describe a patient with AIDS who had developed aggressive KS, which was refractory to the combination of bleomycin, doxorubicin, and vindesin and was also resistant to liposomal daunorubicin. Since paclitaxel has previously demonstrated strong efficacy in patients with KS, we decided to give paclitaxel to this patient [9, 23]. Initially the patient was also taking saquinavir, ritonavir, lamivudine, and stavudine as concomitant therapy. Since the metabolism of paclitaxel and the protease inhibitors occurs predominantly by the same mixed-function oxidase system in the liver, we conducted pharmacokinetics studies in this patient. The paclitaxel AUC was higher and the clearance, thus, lower in the course given without antiretroviral agents, whereas the T > 0.1 μmol/l was substantially longer. Furthermore, no large difference was detected between the drugs with inducing effects on cytochrome P450 enzymes (nevirapine, course 3) and those with inhibitory effects (ritonavir given with saquinavir or indinavir in courses 1 and 6). The paclitaxel pharmacokinetic data altogether did not significantly differ in terms of AUC, C_{max}, and clearance as compared with the pharmacokinetic data reported for non-HIV-1-infected historical controls, to whom paclitaxel had been given at a dose of 100 mg/m^2 as a 3-h infusion [15]. Furthermore, the pharmacokinetics of saquinavir, ritonavir, indinavir, and nevirapine also did not differ from the data reported in the literature [12, 19, 21].

Thus far, only one study has reported preliminary results concerning paclitaxel-indinavir combinations. In that study, no effect of indinavir on paclitaxel pharmacokinetics was found in four patients [7]. It should be noted that dexamethasone was also given as part of the premedication regimen before paclitaxel administration. Dexamethasone is also known to alter the pharmacokinetics of paclitaxel, saquinavir, and ritonavir [12, 22]. With regard to efficacy, it was encouraging to see that paclitaxel showed an impressive effect on this aggressive KS in a patient with an advanced stage of AIDS, which is related to a poor prognosis [17].

Although this was a pharmacokinetics case study involving only one patient, it was unique due to the (clinical) circumstances, because it described the pharmacokinetics of (a) paclitaxel combined with saquinavir/ritonavir, (b) paclitaxel given as a single drug, (c) paclitaxel given together with nevirapine, and (d) paclitaxel given in combination with ritonavir and indinavir. Paclitaxel is an important addition to the drug armamentarium for the treatment of KS. The concomitant use of protease inhibitors and nonnucleoside reverse transcriptase inhibitors may not hamper its combined use. However, as the theoretical consideration for drug-drug interaction cannot be entirely ruled out, it is of great importance that the putative interactions be further explored in well-designed trials.

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