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ORIGINAL ARTICLE

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The pharmacokinetics of liposomal encapsulated daunorubicin are not modified by HAART in patients with HIV-associated Kaposi's sarcoma

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Abstract *Purpose*: To investigate the pharmacokinetics of liposomal daunorubicin (DaunoXome) administered alone or in combination with antiviral therapy including protease inhibitors (PI) to HIV-positive patients affected by Kaposi's sarcoma (KS). *Patients and methods*: A group of 18 patients with extensive or rapidly progressing AIDS-related KS received DaunoXome at a dose of 40 mg/m^2 alone or in association with a triple combination therapy consisting of one PI plus two nucleoside reverse transcriptase inhibitors (NRTI). Daunorubicin pharmacokinetics were determined in a total of 23 cycles, 6 with DaunoXome alone, 9 in combination with indinavir, 6 with ritonavir and 2 with saquinavir. Plasma samples were obtained at different times during the 72 h after DaunoXome administration. Daunorubicin and daunorubicinol plasma levels were determined by high-performance liquid chromatography. *Results*: After the DaunoXome infusion, daunorubicin was rapidly cleared from the body following, in most cases, a one-compartment open kinetic model. The daunorubicin peak concentrations, clearances and elimination half-lives were (means ± SD): 16.3 ± 2.8 μg/ml, 0.3 ± 0.1 l/h per m^2 and 5.6 ± 2.6 h after DaunoXome alone; 15.1 ± 4.9 μg/ml, 0.5 ± 0.3 l/h per m^2 and 5.8 ± 2.1 h after the combination with indinavir; and 14.5 ± 2.8 μg/ml, 0.4 ± 0.2 l/h per m^2 and 6.5 ± 3.9 h after the combination with ritonavir. In all groups, daunorubicinol plasma levels were approximately 25–30 times lower than those of the parent drug. *Conclusion*: Our data show that there are no significant differences in the pharmacokinetic parameters of daunorubicin in patients receiving DaunoXome in combination with indinavir and ritonavir compared with those in patients not receiving PIs. Therefore in patients affected by AIDS-related KS treated with Highly Active AntiRetroviral Therapy (HAART) there is no pharmacokinetic justification for reducing the doses of DaunoXome.

Key words Antiretroviral therapy · Kaposi's sarcoma · Liposomal daunorubicin · Pharmacokinetics · Protease inhibitors

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Introduction

At the present time Highly Active AntiRetroviral Therapy (HAART) is the standard treatment for HIV infection [6, 36, 37] and it is mainly responsible for the marked reductions in morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS) [39, 47]. According to the international guidelines, the combination of a potent protease inhibitor (PI) with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) represents the treatment of choice for HIV-positive patients requiring therapy [6, 36, 37].

Although some authors have noted a reduction in the incidence of Kaposi's sarcoma (KS) in patients treated with HAART, this neoplasm is still the most common AIDS-related malignancy [8, 12, 17, 31]. In addition, the involvement of visceral tissues such as the lungs by KS in HIV-positive patients has often been associated with a poor prognosis [5, 14]. Moreover, in some cases HAART has been able to slow the neoplasm's progression and less frequently even to produce a reduction or disappearance of the typical lesions [1, 3, 7, 21, 25, 27, 35, 40, 49].

The mechanisms of action of antiretroviral treatment on KS still remain largely unknown. The potential mechanisms of antiretroviral therapy invoked by several

authors include HHV8-specific or nonspecific immune effects, decreased expression of Tat protein and direct interaction between HHV8 and HIV [2, 10, 20]. However, systemic therapy with cytotoxic agents is the treatment of choice for patients with extensive or rapidly progressing KS [30, 32]. Various single- and multiagent chemotherapy regimens have been proposed but most of them are burdened by myelosuppression, gastrointestinal toxicity or neuropathy [16, 29, 32]. Recurrent episodes of leukopenia often determine the development of infectious complications. In this context, the introduction of an antiretroviral therapy has often turned out not to be feasible.

Recently, liposomal anthracyclines have been approved for the treatment of advanced HIV-related KS and appear to represent a significant improvement in this field [48]. The anthracycline kinetic modifications induced by liposomal encapsulation of daunorubicin result in a reduced half-life ($T_{1/2}$) and an increased plasma area under the curve (AUC), and consequently limit the drug distribution to the volume of plasma compartment. In contrast, the half-life of anthracyclines with a different liposomal preparation can be prolonged (e.g. the half-life of doxorubicin in Doxil is about 50 h). Liposomal agents selectively accumulate in KS tissues and tumour cells at higher concentrations with enhanced cellular toxicity [13, 28]. Both liposomal doxorubicin and liposomal daunorubicin (DaunoXome) have been shown to be effective and well tolerated [15, 16, 37, 44, 46]. Their relative lack of meaningful adverse events permits the coadministration of highly effective antiretroviral therapy to HIV-positive patients affected by KS.

Cytochrome $P450_{IIIA4}$ (CYP3A4) is the main enzymatic system involved in the metabolism of PIs [11, 41]. Moreover, PIs can potentially inhibit CYP3A4 and therefore modify the pharmacokinetics of drugs metabolized through the same enzymatic pathway [34]. This effect is, however, unlikely to be important as daunorubicin is not mainly metabolized by CYP3A4. In view of the importance of these considerations for a correct clinical management, the potential interactions among antiretroviral compounds and antibiotics, and antifungal and antiviral agents are becoming the subject of a growing number of studies [11, 41, 42].

Until now very few studies have focused on the potential interactions between the antiretroviral agents and the antineoplastic compounds, in spite of the frequent need to combine these classes of drugs in AIDS patients [43, 45]. It was the lack of information that prompted us to undertake this study aimed at evaluating the pharmacokinetics of daunorubicin in patients affected by KS and treated with DaunoXome in combination with HAART.

Patients and methods

Between November 1997 and March 1999, 18 Caucasian patients (17 men and 1 woman) with HIV-positive serology and extensive, rapidly progressing mucocutaneous or visceral KS were enrolled into a pharmacokinetic study at the Department of Infectious Diseases of the San Raffaele Hospital in Milan, Italy.

Patients were eligible to participate in the pharmacokinetic study if they had a biopsy-proven KS, a Karnofsky performance status (KPS) score of 60–70, an absolute granulocyte count (ANC) $> 1000 \times 10^6$/l, platelet count $> 75 \times 10^9$/l, haemoglobin > 10 g/dl and normal renal and hepatic function. At the time of enrolment, all patients were eligible if they had a left ventricular ejection fraction $> 50\%$ calculated by multiple gate acquisition (MUGA) scan. A written informed consent was required for every patient enrolled in the study.

For the study group, the median age at the time of enrolment was 37.5 years (range 29 to 49 years), the median CD4 cell count was 98 cells/μl (range 6 to 440 cells/μl) and the median HIV viral load was $3.87\log_{10}$ copies per milliliter (range < 1.90 to $6.07\log_{10}$ copies per milliliter; Table 1).

Patients were staged for KS in accordance with the NYU disease stage system [22] and with the AIDS Clinical Trials Group (ACTG) classification [23]. Of the 18 patients, 7 had visceral involvement by KS, 5 pulmonary involvement and 2 gastroenteric involvement (Table 1). The diagnosis of pulmonary KS, suspected on clinical or radiological (chest radiography) pulmonary abnormalities, was confirmed by bronchoscopy and chest computerized tomography.

According to the treatment plan, six cycles of DaunoXome were first administered at a dose 40 mg/m^2 every 2 weeks. If the patients achieved a complete response, partial response or a stabilization of the neoplasm (responding criteria according to Krown et al. [23]), they received another three to six cycles of DaunoXome at a dose of 50 mg/m^2 every 3 weeks. Patients with progressing disease after six cycles were considered for other chemotherapeutic regimens.

Seven patients had previously received chemotherapy. A regimen consisting of doxorubicin, bleomycin and vincristine (ABV) had been used in three of the chemotherapy-experienced patients. One patient had been treated with liposomal doxorubicin before the pharmacokinetic study. Nine patients had already been receiving HAART at least 3 months before the beginning of the study.

The liposomal daunorubicin pharmacokinetics were determined in a total of 23 cycles in the following four treatment groups.

- Group A: DaunoXome alone in six patients
- Group B: DaunoXome in combination with indinavir in nine patients
- Group C: DaunoXome in combination with ritonavir in six patients
- Group D: DaunoXome in combination with saquinavir in two patients

To analyse correctly the potential interaction between DaunoXome and HAART, we decided to perform the pharmacokinetic study in patients who had been receiving PIs for at least 1 month. With regard to PIs, patients received indinavir at a dose of 800 mg three times a day, ritonavir 600 mg twice a day and saquinavir (hard-gel) 600 mg three times a day. Two patients in group C received ritonavir at a dose of 400 mg twice a day associated with saquinavir (hard-gel) at 400 mg twice a day. The more commonly used antiretroviral regimen was stavudine, lamivudine and indinavir (Table 1). In five patients we were able directly to compare the pharmacokinetic parameters obtained before and after the beginning of the HAART regimens including indinavir (three patients) or ritonavir (two patients).

The patients received DaunoXome at a dose of 40 mg/m^2 i.v. as a half-hour infusion every 2 weeks on an inpatient basis. In every cycle DaunoXome was infused within 2 h of PI administration.

Pharmacokinetic study

Blood samples were obtained at the end of the infusion and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 h after DaunoXome administration. Separated plasma was heated to 55 °C for 30 min to inactivate HIV and stored at −80 °C until analysis. This inactivation procedure

Table 1 Characteristics of patients and clinical response (*NRTI* nucleoside analogue reverse transcriptase inhibitor, *PI* protease inhibitor; *IDV* indinavir, *NFV* nelfinavir, *RTV* ritonavir, *SQV* saquinavir; *3TC* lamivudine, *D4T* stavudine, *ZDV* zidovudine; *ABV* doxorubicin, bleomycin and vincristine, *ADM* doxorubicin, *BLM* bleomycin, *VCR* vincristine, *VP-16* etoposide; *CR* complete response, *PR* partial response, *Prog* progression, *SD* stable disease); *n.a.* not assessable (patient lost to follow-up)

Patient no.	Sex	Age (years)	CD4 count (cells/μl)	HIV-RNA (log_{10} copies/ml)[a]	Ongoing antiretroviral therapy		Previous therapy		Disease stage		Clinical response[c]
					PIs	NRTIs	PIs	KS chemotherapy	NYU[b]	TIS[c]	
1	Male	33	36	5.81	IDV	D4T, 3TC	IDV	BLM + VCR	III	T1 I1 S0	SD
2	Male	34	154	13.14	SQV, RTV	D4T	SQV	BLM + VCR	III	T1 I1 S1	PR
3	Male	46	86	4.96	SQV	ZDV, 3TC	SQV	Liposomal ADM	IV (lung)	T1 I1 S1	CR
4	Male	33	11	3.65	SQV	D4T, 3TC	No	No	IV (lung)	T1 I1 S1	PR
5[e]	Male	49	274	5.08	IDV	D4T, 3TC	No	No	IV (gastroenteric)	T1 I1 S1	Prog
6	Male	42	53	3.47	SQV, RTV	D4T	SQV	No	III	T1 I1 S1	PR
7[d]	Male	36	110	5.00	RTV	D4T, 3TC	No	No	IV (lung)	T1 I1 S0	PR
8[d]	Male	39	49	6.07	IDV	D4T, 3TC	No	No	III	T1 I1 S0	PR
9	Female	44	112	3.07	IDV	D4T, 3TC	No	ABV	III	T1 I0 S0	PR
10	Male	42	44	2.47	IDV	ZDV, 3TC	No	No	III	T1 I1 S0	PR
11[d]	Male	33	440	3.83	IDV	D4T, 3TC	No	No	III	T1 I0 S0	CR
12	Male	35	330	3.90	IDV	D4T, 3TC	No	ABV, BLM, VP-16	III	T1 I0 S0	SD
13	Male	49	311	3.07	RTV	D4T, DDI	NFV	No	III	T1 I1 S0	PR
14[d]	Male	29	13	3.44	IDV	D4T, 3TC	No	No	IV (gastroenteric)	T1 I1 S0	PR
15	Male	40	187	4.73	IDV	D4T, 3TC	RTV	No	III	T1 I1 S0	PR
16[e]	Male	41	150	5.77	RTV	D4T	RTV	No	IV (lung)	T1 I1 S1	PR
17	Male	34	85	< 1.90	RTV	D4T, 3TC	RTV	ABV	III	T1 I1 S1	n.a.
18[d]	Male	32	6	5.70	RTV	ZDV, 3TC	SQV	No	IV (lung)	T1 I1 S0	PR

[a] Plasma viral load was analyzed by nucleic acid sequence-based amplification (NASBA); the limit of detection was 80 copies/ml
[b] See [22]
[c] Tumor (T), Immune system (I), Systemic illness (S); see [23]
[d] Patients in whom it was possible to obtain pharmacokinetic data before and after the beginning of HAART
[e] Patients in whom pharmacokinetics were repeated after 9 and 15 cycles of DaunoXome

does not affect the stability of either daunorubicin or daunorubicinol (data not shown). The pharmacokinetic assays were done at the Department of Oncology of the Istituto Mario Negri in Milan. Daunorubicin and daunorubicinol were determined in plasma by high-performance liquid chromatography (HPLC) with fluorimetric detection in accordance with a previously described method [4] with minor modifications.

A 0.5–1 ml aliquot of plasma and 1 μg doxorubicin as internal standard were mixed with 1 ml borate buffer, pH 8.4, followed by deproteinization with $AgNO_3$ (33%), extraction with 8 ml chloroform and centrifugation at 3500 rpm. The separated organic phase was evaporated under vacuum and the residue was dissolved in 0.1 *M* phosphoric acid and 50 μl was injected into the HPLC system (501 module; Waters, Milford, Mass.). Fluorescence detection was at an excitation wavelength of 475 nm and an emission wavelength of 580 nm (Model 474, Waters). Separation was achieved with an isocratic solvent system of acetonitrile/water/0.1 *M* phosphoric acid (30:44:26) at a flow rate of 1.5 ml/min using a μBondapak C18 column, 4.6 × 30 mm (Waters). The limit of quantitation for both daunorubicin and daunorubicinol was 5 ng/ml.

Calculations

The experimental plasma AUC (area under the curve of concentration versus time) was calculated using the trapezoidal rule from 0 to 72 h and half-life ($T_{1/2}$), plasma clearance (Cl_p) and volume of distribution (V_d) were calculated using the formulas $T_{1/2} = \ln 2/K$, Cl_p = dose/AUC and $V_d = Cl_p/K$, where K is the elimination rate constant indicating the slope of the terminal phase of the weighted plasma concentration data versus time curve calculated using a general nonlinear fitting program [24].

Statistical analysis

The pharmacokinetic parameters of the different groups were compared using Student's *t*-test.

Results

After the DaunoXome infusion, daunorubicin was rapidly cleared from the body following, in most cases, a one-compartment open kinetic model (Fig. 1). Table 2 shows the main pharmacokinetic parameters of daunorubicin and daunorubicinol in patients who received DaunoXome alone or in combination. The daunorubicin peak concentrations (C_{max}), clearances (Cl_p), elimi-

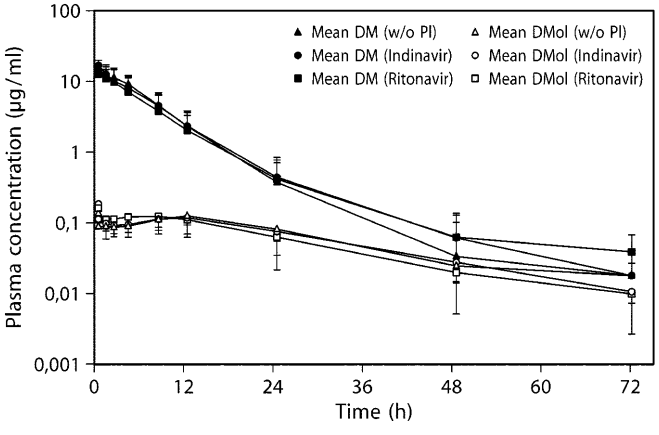

Fig. 1 Mean (+SD) plasma daunorubicin (*DM*) and daunorubicinol (DMol) concentrations over the 72 h following treatment with DaunoXome 40 mg/m^2 alone ($n = 6$) and in combination with indinavir ($n = 9$) or ritonavir ($n = 6$)

Table 2 Main pharmacokinetic parameters of daunorubicin and daunorubicinol after DaunoXome administration at 40 mg/m^2 with and without PI (C_{max} peak concentration, μg/ml; AUC_{exp} experimental area under the curve, μg/ml · h; $T_{1/2}$ elimination half-life, h; Cl_p clearance, l/h/m^2; V_d volume of distribution, l/m^2)

		Daunorubicin					Daunorubicinol		
		C_{max}	AUC_{exp}	$T_{1/2}$	Cl_p	V_d	C_{max}	AUC_{exp}	$T_{1/2}$
DaunoXome without PI ($n = 6$)	Mean	16.36	114.91	5.6	0.39	3.2	0.15	5.12	19.44
	SD	2.84	41.94	2.6	0.17	1.6	0.04	2.15	12.56
DaunoXome + indinavir ($n = 9$)	Mean	15.12	106.86	5.8	0.50	4.2	0.18	4.22	14.81
	SD	4.97	47.90	2.1	0.36	1.4	0.05	1.91	2.48
DaunoXome + ritonavir ($n = 6$)	Mean	14.53	100.96	6.5	0.46	4.3	0.17	3.56	14.90
	SD	2.82	46.28	3.9	0.20	1.0	0.04	1.27	2.29

nation half-lives ($T_{1/2}$) and volumes of distribution (V_d) were (means ± SD) 16.3 ± 2.8 μg/ml, 0.3 ± 0.1 l/h per m^2, 5.6 ± 2.6 h and 3.2 ± 1.6 l/m^2 ($n = 6$) after DaunoXome alone; 15.1 ± 4.9 μg/ml, 0.5 ± 0.3 l/h per m^2, 5.8 ± 2.1 h and 4.2 ± 1.4 l/m^2 ($n = 9$) after DaunoXome in combination with indinavir; and 14.5 ± 2.8 μg/ml, 0.4 ± 0.2 l/h per m^2, 6.5 ± 3.9 h and 4.3 ± 1.0 l/m^2 ($n = 6$) after DaunoXome in combination with ritonavir. In the two patients (numbers 3 and 5) who received the combination with saquinavir, the daunorubicin clearances were 0.35 and 1.1 l/h per m^2, respectively. In all groups, daunorubicinol plasma levels were approximately 25–30 times lower than those of the parent drug.

No significant differences were found in the pharmacokinetic parameters of daunorubicin and the metabolite between the study groups ($P > 0.05$). An intrasubject comparison of the pharmacokinetics was made in five patients. No significant changes were found in three patients who received DaunoXome alone and in combination with indinavir. In two patients who received ritonavir we found a 30% decrease in the experimental AUC in comparison with the AUC found after the administration of the DaunoXome alone.

We also looked at the effect of previous chemotherapy on the pharmacokinetics of DaunoXome, comparing a group of 12 patients who had never received cytotoxic agents with a group of 8 patients who had received at least six cycles of chemotherapy (Table 1). The latter group included two patients in whom it was possible to obtain the pharmacokinetic data at the beginning and after 9 and 15 cycles of DaunoXome. None of the previously treated patients showed abnormal liver or kidney function. As Table 3 shows, previous chemotherapy significantly affected the pharmacokinetics of daunorubicin. In particular, the AUC_{exp} and Cl_p were (means ± SD) 139.1 ± 36.6 μg/ml · h and 0.3 ± 0.1 l/h per m^2, respectively, in pretreated patients and 90.8 ± 48.7 μg/ml · h and 0.6 ± 0.3 l/h per m^2 in unpretreated patients. The difference was statistically significant ($P = 0.03$).

With regard to toxicity, we compared the occurrence of severe (grade 3 or 4) adverse events in 6 patients treated with DaunoXome for a total of 9 cycles and in 18 patients treated with DaunoXome plus HAART for a total of 45 cycles. No patient discontinued treatment because of drug toxicity. The most common adverse event was leukopenia which occurred in one cycle (11.1%) without antiretroviral therapy and in six cycles (13.3%) with antiretroviral therapy. The difference was not significant at the 5% level. Granulocyte colony-stimulating factor (G-CSF) was utilized in 15% of cycles. Only a patient treated with HAART developed severe anorexia during the second cycle of chemotherapy with DaunoXome in combination with HAART. In subsequent cycles, this patient was able to continue the antiretroviral therapy. Altogether, chemotherapy with DaunoXome did not seem to influence compliance with antiretroviral therapy. Pretreatment and posttreatment (240 mg/m^2) estimates of left ventricular ejection fractions >50% calculated by MUGA scan were obtained in 50% of the study patients. No patient experienced a reduction in ejection fraction below 50%.

Discussion

The need to maintain adequate immunity while providing the patients with cytotoxic chemotherapy represents one of the most crucial challenges posed by

Table 3 Pharmacokinetic parameters of daunorubicin and daunorubicinol following treatment with DaunoXome at 40 mg/m^2 in patients previously treated or not previously treated with chemotherapy (C_{max} peak concentration, μg/ml; AUC_{exp} experimental area under the curve, μg/ml · h; $T_{1/2}$ elimination half-life, h; Cl_p clearance, l/h/m^2; V_d volume of distribution, l/m^2)

		Daunorubicin					Daunorubicinol		
		C_{max}	AUC_{exp}	$T_{1/2}$	Cl_p	V_d	C_{max}	AUC_{exp}	$T_{1/2}$
Pretreated ($n = 8$)	Mean	18.12	139.2	5.7	0.30	2.4	0.17	4.88	15.70
	SD	4.18	36.7	1.6	0.06	0.7	0.03	1.46	1.54
Not pretreated ($n = 12$)	Mean	14.50	90.8	5.6	0.60	4.8	0.15	3.97	16.03
	SD	4.57	48.7	4.5	0.36	2.5	0.04	2.23	9.38

HIV-related malignancies. It often happens that the oncologist is faced with the dilemma of instituting or continuing the use of PIs in combination with chemotherapy. Some authors have expressed concern regarding the emergence of resistant strains of HIV-1 when antiretroviral therapy is withheld while the patient receives antineoplastic treatment [45]. This issue can be addressed in different ways. Recently, Little et al. have demonstrated that it is possible to stop HAART in HIV-positive patients while they are receiving EPOCH chemotherapy for non-Hodgkin's lymphoma without compromising postchemotherapy immune recovery or HIV control by means of HAART [26]. In order to optimize the combination of antiretroviral therapy and anticancer drugs it is necessary to obtain pharmacokinetic data to evaluate any potential interactions. Since single-agent chemotherapy is standard treatment for AIDS-related KS, strategies to combine anti-KS chemotherapy with multiagent antiretroviral therapy may be easier to study in terms of pharmacokinetic interactions than those involving multiple antiretroviral drugs given simultaneously with multiple anticancer drugs.

In this study we evaluated the interaction between DaunoXome and HAART in patients with AIDS-related KS. DaunoXome was selected because it is widely used in patients with AIDS-related KS owing to its relatively good efficacy and tolerability. The study showed that antiretroviral therapy consisting of two NRTIs and one PI did not modify DaunoXome pharmacokinetics. When patients were given ritonavir or indinavir in combination with the DaunoXome, no significant modifications of plasma C_{max}, AUC, $T_{1/2}$, Cl_p or V_d of daunorubicin were found in comparison with patients not treated with PI. Too few patients receiving saquinavir in combination with DaunoXome were analyzed to draw any conclusion regarding this combination. The pharmacokinetic parameters found were similar to those previously reported in cancer patients during phase I/II trials with DaunoXome [15, 16, 19]. As noted with other cytotoxic agents [9, 33], previous chemotherapy seemed to affect the kinetics of liposomal daunorubicin since we found a weak but significantly higher AUC in previously treated patients than in untreated patients.

Although it was not the aim of the present study to obtain a clinical evaluation of the anticancer effect of DaunoXome associated with HAART, out of 17 assessable patients a complete or partial response was documented in 14 (82.3%). Remarkably, chemotherapy was able to be stopped in ten patients with severe debilitating disease, three of them with pulmonary lesions, after 9–18 cycles with DaunoXome. With regard to pulmonary KS our findings are consistent with the significant prognostic improvement recently reported by others who have used either DaunoXome or HAART singly [1, 18, 29, 46]. The HAART-DaunoXome combination was usually well tolerated and patients suffered few episodes of leukopenia controlled by the use of colony-stimulating factors. So far none of the patients has developed opportunistic infections.

In conclusion, our results show that patients affected by extensive or rapidly progressing AIDS-related KS can receive an antiretroviral therapy consisting of indinavir or ritonavir plus two NRTIs in combination with DaunoXome without significant modification of the pharmacokinetic parameters of the cytotoxic compound. The lack of pharmacokinetic interaction is consistent with the absence of an increase in toxicity of the combination regimens which appeared to be well-tolerated by patients. However, it should be stressed that the potential pharmacokinetic impact of the liposomal daunorubicin on the antiretroviral drugs was not assessed in our study.

Although the present study does not allow us to draw any conclusion as to the effectiveness of the antiretroviral-chemotherapy combination against extensive AIDS-related KS, control of the neoplasm was seen in most patients, even in the presence of pulmonary involvement.

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