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Short report

Effect of cyclosporine on teniposide pharmacokinetics and pharmacodynamics in patients with renal cell cancer

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Five patients with metastatic renal cell cancer (RCC) entered this study. The patients received two courses of teniposide (VM26) (200 mg/m^2/24 h i.v.) after which no objective response was observed: three patients had stable disease (SD) and two had progressive disease. Cyclosporine (CsA) (5 mg/kg/2 h followed by 30 mg/kg/48 h i.v.) was then added (VM26/CsA) and at least another two courses were administered. Pharmacokinetic and pharmacodynamic parameters were analyzed. CsA increased the area under curve (AUC) of VM26 in four out of five patients; on average, the variation in the paired AUC of VM26 was 41%. Nadir granulocyte count was lower (average 650/mm^3, ranging from <100 to 1800/mm^3) after VM26/CsA than after VM26 (average 1260/mm^3, ranging from 200 to 2100/mm^3) ($p < 0.01$). Bilirubin concentration in the serum was increased after VM26/CsA compared with VM26 ($p < 0.05$). Finally, after two courses of VM26/CsA, four patients had stable disease and one patient had a minor response. In conclusion, the ongoing pilot study indicates that CsA affects both the pharmacokinetics and the pharmacodynamics of VM26.

Key words: Cyclosporine, MDR, renal cell cancer, teniposide.

Introduction

Renal cell cancer (RCC) is a tumor resistant to chemotherapy. There is no active cytotoxic chemotherapy, conventionally accepted, for patients with this malignancy. In fact, the objective response has a rate less than 9% and is usually of short duration.[1] A partial, biologic explanation of this intrinsic refractoriness to the drug may be related to the expression of multidrug resistance (MDR)-associated P170 glycoprotein (P-gp) on the RCC cell surface. Elevated MDR1 mRNA levels in the proximal tubule cells of normal kidney have been described[2] and strong MDR1 gene expression has been shown in most RCCs.[3] Previous studies have demonstrated that cyclosporine (CsA) can competitively inhibit P-gp activity and modulate MDR in *in vitro* experimental models[4] and human tumors.[5] Besides the effect on tumor cells, MDR modulators can affect the pharmacokinetics and pharmacodynamics of antineoplastic drugs.[5] Lum *et al.*[6] reported that CsA increased etoposide AUC and bilirubin concentration in the serum. The effects of CsA on the pharmacokinetics and pharmacodynamics of mitoxantrone,[7] daunorubicin,[8] vinblastine[9] and doxorubicin[10] have also been reported.

To the best of our knowledge, nothing is known about the effect of CsA on the pharmacokinetics and pharmacodynamics of VM26. The aim of the present study was to investigate this issue.

Materials and methods

Patients with a pathologically verified diagnosis of RCC and progressive disease after previous chemotherapy were eligible for this study. Approval of the study was obtained from the Ethical Committee of the Institute. Informed consent was required prior to the patients' entry into the study. Five patients (male female, 4 1; median age 60, range: 52–70 years) were selected for this study. All but one patient had been previously treated with immunother-

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apy (interleukin-2 and/or interferon-α) and had disease progression. One patient with unresectable primary tumor had disease progression after medroxyprogesterone acetate. Median WHO performance status was 1 (range: 1–2). Patients were first administered teniposide (Vumon; Bristol Myers, Sermoneta (LT), Italy), 200 mg/m^2/24 h i.v. every 3 weeks. After two courses of therapy, the patients were evaluated for response by chest X-rays or ultrasound, depending on the site of the disease. Patients whose tumors responded continued to receive VM26 until tumor progression occurred. Those patients with tumor progression or stable disease after two courses of VM26 were treated with the combination of CsA (Sandimmune; Sandoz, Basilea, Switzerland) and VM26 (VM26/CsA). CsA was administered initially as an i.v. loading dose during a 2 h period (5 mg/kg) followed by i.v. continuous infusion for 48 h (15 mg/kg/24 h) (h 0–48) together with i.v. infusion of VM26 (h 0–24). The data concerning hematological and biliary toxicity refer to the first course with VM26 and to the first course with VM26/CsA. Patient evaluation included complete blood cell counts, and serum bilirubin and creatinine concentration at study entry; the evaluation was performed daily during treatment and then weekly until subsequent treatment. VM26 plasma concentration was measured in the patients during the first course of VM26 as a single agent and during the first course of VM26/CsA with the same sampling schedule. Samples were collected from a peripheral vein before the onset of infusion (h 0) and at h 1, 6, 12, 18, 24, 24.5, 25, 26, 28, 32, 36, 48 and 60. VM26 was extracted from the plasma and the concentration was measured by HPLC.[11] Blood samples from analysis of CsA were collected at h − 2, 0, 6, 12, 24, 36, 48, 60 and 72. The measurements were performed on hemolyzed plasma by a non-specific fluroescence polarization immunoassay that cross-reads with both CsA and metabolites (TDx; Abbott, Rome, Italy). The kinetic parameters of VM26 were estimated by the non-linear regression program PCNONLIN 4.0. Comparison between the parameters of VM26 and VM26/CsA was made by the *t*-test for paired data.[12]

Results

All five patients received two courses of VM26 after which three patients had stable disease and two had progressive disease. Subsequently, the patients were administered VM26/CsA; the total number of courses administered was 21 (median number 4, range: 2–6). All courses were administered according to the treatment protocol. After two courses with VM26/CsA, four patients had stable disease and one patient had a minor response documented by chest X-rays at the mediastinal level. Data on duration of stabilization are not yet available. Kinetic parameters of VM26 administered alone or together with CsA are reported and compared in Table 1. Individual concentrations of CsA at the end of infusion are reported in Table 2.

Treatment with VM26 alone was generally well tolerated. One patient had leucopenia G3 and one had leucopenia G4. This latter developed also neutropenia fever (Table 2, patient 4). By contrast, administration of VM26/CsA was associated with moderate nausea and vomiting (two patients), prolonged sensation of heat (three patients) and epigastric pain (one patient). Heat and epigastric pain were ascribable to CsA. The individual values of nadir granulocyte count (ANC) decreased after VM26/CsA compared to VM26 alone ($p < 0.01$) and a significant correlation ($r = -0.88$; $p < 0.01$) between the nadir of ANC and the AUC of VM26 was found. Other side-effects observed after VM26/CsA were G2 mucositis (two patients) and transaminases elevation (one patient). Finally, bilirubin in the ser-

Table 1. Kinetic parameters of VM26 administered alone and together with CsA (VM26/CsA) in five patients

Treatment	C_{max} (mg/l)	AUC (mg/lh)	V (l/m^2)	$t_{1/2}$ (h)	Cl (l/m^2/h)
VM26 (mean ± SD)	17.6 ± 3.9	470 ± 188	6.9 ± 3.3	10 ± 3.1	0.55 ± 0.28
VM26/CsA (mean ± SD)	22.3 ± 7.9	665 ± 280	7.4 ± 4.4	15.9 ± 6.2	0.45 ± 0.37
Change (%)	+27	+41	+7	+59	−19
p[a]	NS[b]	< 0.05	NS	NS	NS

[a] *t*-test for paired data;
[b] NS, not significant ($p > 0.05$).

Table 2. Values of the nadir granulocyte count (ANC), total bilirubin (Bil) after the first course with VM26 and after the first course with VM26/CsA, and blood concentrations of CsA at the completion of infusion

Patient no.	ANC nadir VM26 ($\times 10^3/\mu l$)	ANC nadir VM26/CsA ($\times 10^3/\mu l$)	[Bil][a] VM26 (mg/dl)	[Bil][a] VM26/CsA (mg/dl)	[CsA] (ng/ml)
1	1.6	< 0.1	0.6	6.1	6100
2	1.7	0.7	0.4	2.6	6440
3	0.7	0.6	0.5	1.4	6470
4	0.2	0.1	0.5	5.2	5500
5	2.1	1.8	0.4	1.0	4760
	$p < 0.01$[b]		$p < 0.05$[b]		

[a] Highest concentration of bilirubin observed during the infusion with CsA and on the day after completion of drug infusion.
[b] *t*-test for paired data.

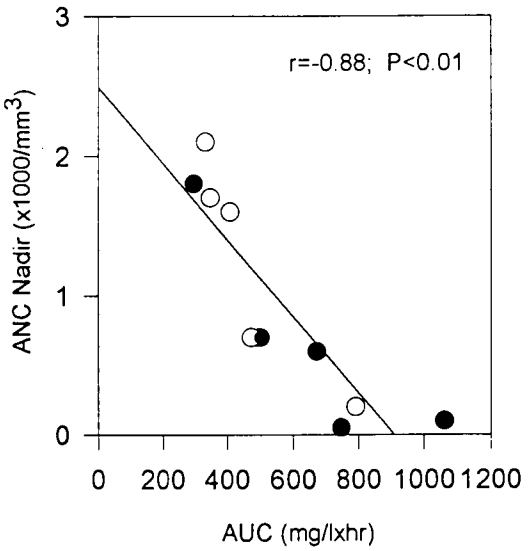

Figure 1. Correlation between AUC of VM26 and nadir granulocyte counts (ANC) in patients treated with VM26 alone (○) or supplemented with CsA (●); the correlation is pointed out by the regression line.

um was increased after VM26/CsA compared to VM26 alone ($p < 0.05$) (Table 2). Hyperbilirubinemia due to CsA (Table 2) was rapidly reversible after the completion of CsA infusion. In agreement with previously reported data,[13] we did not observe cumulative toxicity during the first two courses with VM26 alone or with VM26/CsA.

Discussion

Intrinsic high levels of P-gp expression may contribute to confer drug resistance to RCC, therefore modulation of MDR may improve the efficacy of pharmacological treatments. On these grounds, combined VM26 plus CsA treatment was selected to treat patients with RCC not responsive to VM26 alone (a drug involved in MDR).[14] Blood concentration of CsA in the five patients analyzed ranged from 2800 to 6400 ng/ml during the 48 h of i.v. infusion. These levels of CsA were effective *in vitro* in reverting MDR[4] (and our unpublished results).

The small number of patients evaluated and the lack of a striking difference in the response rate between treatments with or without CsA did not allow us to draw definitive conclusions on the efficacy of CsA as a chemosensitizer of VM26 cytotoxicity in RCC. However, our data clearly indicate that CsA affects both the pharmacokinetics and the pharmacodynamics of VM26. In fact, an increase in the mean $t_{1/2}$ (59%) and plasma AUC of VM26 (41%) was observed adding CsA to VM26 ($p < 0.01$). Moreover, VM26/CsA treatment increased both myelosuppression and bilirubin concentration in the serum as compared with the treatment with VM26 alone. It is worth considering that P-gp is expressed in normal tissues and has a potential function in the excretion of antineoplastic drugs or other substrates such as bilirubin into both the bile and urine.[14] This led to the hypothesis that the hyperbilirubinemia observed after CsA exposure could be due to the modulation of P-gp activity in biliary canaliculi of the liver.[14] However, we think that modulation of P-gp activity by CsA in biliary canaliculi and in proximal renal tubules has a marginal role in the increase of AUC concentration of VM26 after CsA administration. This is because renal and biliary excretion of VM26 represent a small part of the total elimination of the drug.[15] The increase in AUC of VM26 could be related to an altered metabolism of the drug. Recently, Relling *et al.*[16] reported that CsA could in-

terfere with the *O*-demethylation of VM26 mediated by cytochrome P450 3A4. CsA is a substrate for this cytochrome and inhibits catechol formation from VM26.

Finally, the increased myelosuppression associated with VM26/CsA administration compared with treatment with VM26 alone is likely explained by the increased AUC after VM26/CsA exposure. Moreover, it must be considered that P-gp is expressed in normal hemopoietic stem cells[2] and CsA inhibition of P-gp activity could enhance bone marrow toxicity of VM26. In conclusion, this ongoing study demonstrates that CsA affects both the pharmacokinetics and pharmacodynamics of VM26 in patients with metastatic RCC.

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