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Standard Pentostatin Dose Reductions in Renal Insufficiency are not Adequate: Selected Patients with Steroid-Refractory Acute Graft-versus-Host Disease

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Abstract

Background and Objective—Pentostatin is an irreversible inhibitor of adenosine deaminase and has been used to prevent graft-versus-host disease (GVHD) and to treat both acute and chronic GVHD. Dose reduction equations for patients with renal insufficiency are based on few patients with limited pharmacokinetic and clinical results. This phase II study (NCT00201786) was conducted to assess pentostatin efficacy and infectious complications seen from our previous phase I study in steroid-refractory acute GVHD (aGVHD).

Patients and Methods—Hospitalized patients with steroid-refractory aGVHD were given pentostatin 1.5 mg/m²/day intravenously on days 1–3 of each 14 day cycle. Prior to each dose, dose modifications were based on Cockcroft-Gault estimated creatinine clearance (eCrCL) with 30–50 ml/min/1.73m² leading to a 50% dose reduction and eCrCL < 30 ml/min/1.73m² leading to study removal. Plasma pentostatin area under the concentration-time curve (AUC) and incidence of infectious complications were evaluated.

Results—Two of the eight patients treated demonstrated excessive pentostatin exposure as determined by measurement of AUC. One of these patients had renal impairment while the other patient demonstrated borderline renal function. Despite dose reduction to 0.75 mg/m², AUCs were

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significantly increased compared to the other patients in this study. Seven of eight patients treated with pentostatin had cytomegalovirus (CMV) viremia after pentostatin treatment; however none developed proven CMV disease.

Conclusion—A 50% dose reduction in patients with eCrCL 30–50 ml/min/1.73m² seems reasonable. However, the eCrCL should be interpreted with extreme cautions in patients who are critically ill and/or with poor performance status. Renal function assessment based on the Cockcroft-Gault method could be significantly overestimated thus risking pentostatin over-dosing. These results imply a need to closely monitor pentostatin exposure in patients with renal insufficiency.

Background

Pentostatin (deoxycoformycin, Nipent) is an irreversible inhibitor of adenosine deaminase that has been reported to successfully prevent murine graft-versus-host disease (GVHD).^[1] As a result, this agent has been incorporated into stem cell transplant conditioning regimens in humans as part of reduced intensity regimens^[2] and has been studied in the treatment of both acute and chronic GVHD.

Lymphocytes are especially sensitive to the effects of pentostatin, as it irreversibly inhibits adenosine deaminase, blocking the metabolism of 2'-deoxyadenosine. Patients with inherited adenosine deaminase deficiency have few T-cells and have a form of severe combined immunodeficiency.^[3] Treatment with pentostatin creates a similar condition^[4] by causing a decrease of T-cell response to interleukin-2 (IL-2) and IL-2 production by T-cells, a reduction in T-cell number and function, antibody- and non-antibody-dependent cytotoxicity, and a decrease of natural killer cell numbers and lymphocyte count.^[5–8]

We previously reported a phase I trial of pentostatin in the treatment of steroid-refractory acute GVHD (aGVHD) to determine safety and tolerability of this purine nucleoside analog with minimal myelosuppression. Results were promising with 55% of patients achieving a complete response and 15% achieving a partial response,^[9] but at doses higher than 2 mg/m²/day for 3 days, patients developed excessive late infections. We concluded that a dose of 1.5 mg/m² for 3 doses was appropriate and that the dose should be reduced in patients with renal impairment.

With these results, we performed a follow-up phase II study in patients with steroid-refractory aGVHD to better assess efficacy and pharmacokinetic of pentostatin. Although the study was terminated by the sponsor after eight patients were enrolled, new data regarding infectious complications and pharmacokinetic parameters in patients with renal insufficiency are reported here and are pertinent as pentostatin is used currently in the treatment of patients with hematologic malignancies, and within the preparative regimen as GVHD prophylaxis.

1. Methods

2.1 Study eligibility

Patients were required to have biopsy-proven grade II–IV^[10] aGVHD following related (5/6 or 6/6 matching loci by serologic typing) or unrelated (matched for at least human leukocyte antigens (HLA) A, B and DRB1 by molecular typing) allogeneic stem cell transplant or donor lymphocyte infusion that was refractory to 1 mg/kg/day of intravenous methylprednisolone. Steroid-refractory aGVHD was defined by progression after 72 hours of therapy, persistence of grade II aGVHD after 5 days, incomplete response after 2 weeks, or recurrence after complete response during steroid taper despite restarting corticosteroids for 5 days. This definition is based on the previous report that patients who do not respond

by day 5 of therapy with methylprednisolone have an increased mortality.^[11] For enrollment, patients were required to have an absolute neutrophil count of $\geq 500/\mu\text{L}$, a creatinine clearance $\geq 30 \text{ ml/min/1.73m}^2$, ECOG performance status ≤ 4 , and no uncontrolled infection (must have been off therapeutic antibiotics for at least 72 hours), except for cytomegalovirus (CMV) viremia without disease for which treatment was required for at least 5 days. After patients provided written, informed consent and eligibility was confirmed, the study was conducted according to the principles outlined by the 18th World Medical Assembly (Helsinki, 1964) and FDA regulations regarding the protection of human subjects. This trial was registered at www.clinicaltrials.gov as #NCT00201786.

2.2 Treatment

Patients received pentostatin $1.5 \text{ mg/m}^2/\text{day}$ intravenously over 20–30 minutes with one liter hydration on days 1–3 of each 14 day cycle. Prior to each infusion, dose modifications were considered based on Cockcroft-Gault estimated creatinine clearance (eCrCL)^[12] of 30–50 ml/min/1.73m^2 leading to a 50% dose reduction and $\text{eCrCL} < 30 \text{ ml/min/1.73m}^2$ leading to study removal. Patients were started on prophylactic trimethoprim/sulfamethoxazole 160/800 mg twice daily twice weekly, and acyclovir 200–400 mg three times daily or equivalent. CMV prophylaxis with foscarnet was recommended but not required to avoid additional myelosuppression, and invasive fungal prophylaxis was required with voriconazole, intraconazole, amphotericin B, or caspofungin. Other immunosuppressive agents that patients were receiving at the time of study entry for the primary therapy of GVHD (e.g. cyclosporine, tacrolimus, mycophenolate mofetil) were continued.

2.3 GVHD assessment and response criteria

Acute GVHD was scored by the use of the consensus criteria.^[10] Biopsies of all involved organs were required to corroborate the clinical diagnosis of aGVHD. The exception included patients with multi-organ aGVHD where liver biopsy was preferred but not required; liver-only GVHD required biopsy confirmation.

Response was assessed every 7 days while on treatment. A complete response (CR) required resolution of all signs and symptoms of GVHD in all organs without intervening salvage therapy. A partial response (PR) was an improvement of one stage in one or more organs without progression in any organ. Mixed response was considered an improvement in at least one organ with progression or newly developed GVHD in another organ(s). No response was defined as absence of improvement or deterioration within 14 days of therapy initiation. Progression was defined as worsening by one or more stages without improvement in any involved organ. Toxicity, infections, and GVHD flares (increase in symptoms or therapy for aGVHD after an initial response) were recorded through day 90. All toxicities were reported regardless of attribution to the study treatment. Adverse events (AE) were evaluated according to National Cancer Institute Common Terminology Criteria for AEs, version 2.0.

2.4 Pharmacokinetic studies

Five mL venous whole blood samples were collected in purple top (EDTA) tubes prior to pentostatin administration (day 1 only), and at 5- and 10- min and 2-, 6-, 8- and 24-hours after the end of infusion for each of the first three daily doses during the first course of treatment. Twenty-four hour specimens on day 2 and 3 were drawn prior to start of infusion for those days (a total of 19 samples were collected for a complete first course). Blood samples were centrifuged, and plasma was stored at -80°C until analysis. Plasma pentostatin concentrations were determined as previously described.^[13, 9] Briefly, pentostatin concentrations were determined with an adenosine deaminase inhibition assay measuring the conversion of adenosine to inosine via ultra-violet (UV) absorbance.

Concentration-time profiles were analyzed and pharmacokinetic parameters estimated using non-compartmental methods performed in WinNonlin Professional (version 5.2; Pharsight Corp., Cary, NC, USA).

3. Results

3.1 Demographics

Patient demographics and transplant characteristics are summarized in Table I. All patients received standard prophylaxis for aGVHD. Patients receiving cyclosporine received 3 mg/kg/day intravenous cyclosporine commencing on day -1 and short-course methotrexate 15 mg/m² day 1 and 10 mg/m² days 3, 6, and 11. Patients receiving tacrolimus with methotrexate received 0.03 mg/kg/day intravenous tacrolimus commencing on day -2. For patients #7 and #8, infliximab was administered as a 120-minute infusion at 10 mg/kg the day before the conditioning regimen as part of a clinical trial investigating infliximab's activity in GVHD prophylaxis; five subsequent doses were given on days 0, 17, 114, 128, and 142.^[14]

Six male and two female Caucasian, non-Hispanic patients with a median age of 48 years (range, 22 to 63) were enrolled and treated. Mean and median eCrCL were 88.7 ± 26.3 and 89.9 (48.7–135.8) ml/min/1.73m², respectively. The number of courses of treatment completed ranged from 0.66 (2 of 3 doses) to 3, and the number of total doses received ranged from 2 to 9.

3.2 Clinical course

Treatment and response data are summarized in Table II. Patients #1, #7, and #8 all developed early-onset aGVHD with involvement of the gut and liver. All had improvement of their diarrhea with pentostatin treatment, but their total bilirubin increased and all three patients died approximately three weeks after starting salvage pentostatin due to progressive hepatic GVHD.

Patients #3 and #4 received donor lymphocyte infusions for poor engraftment at day +68 and developed aGVHD approximately 3 and 5 weeks later, respectively. Patient #3 initially had a stable response but total bilirubin continued to trend up and clinical course was complicated by multiple infections including CMV viremia, *Streptococcus milleri* bacteremia, methicillin-sensitive *Staphylococcus aureus* bacteremia, and vancomycin-resistant *Enterococcus faecium* central-venous catheter colonization. These infections along with progressive hepatic GVHD and pancytopenia may have predisposed the patient to multisystem organ failure. Patients #4 and #6 received three and two cycles of pentostatin, respectively but ultimately progressed with hepatic GVHD. None of the patients with hepatic GVHD responded to pentostatin; two patients underwent liver biopsy but none met the criteria for hepatic sinusoidal obstruction syndrome.^[15]

Patient #5 received all three doses, but the third dose was reduced by 50% due to rising serum creatinine and eCrCL of < 50 ml/min/1.73m². The day after pentostatin was completed; the patient became hypotensive from gram-negative sepsis and was intubated for hypercapneic hypoxemic respiratory failure. Care was withdrawn four days later due to acute renal failure and progressive multisystem organ failure.

The only survivor, patient #2, had a persistent rash with bullous formation despite approximately one month of steroid treatment. This patient responded well to pentostatin. Seven of eight patients treated with pentostatin had CMV viremia after pentostatin treatment, although no patients developed proven CMV disease.

3.3 Pharmacokinetic analysis

Plasma pentostatin concentrations were measured for the first course of treatment in all eight patients. A total of 23 doses were administered during course 1 (one patient did not receive the 3rd dose) providing 146 plasma samples for pentostatin concentration determination and 23 concentration-time profiles. A summary plot including data for all patients expressed as a 72-hour time course for the three consecutive doses relative to the start-of-infusion for each dose is shown in Figure 1 which includes all measurable concentrations. All pre-dose measurements are displayed at time zero. Non-compartmental pharmacokinetic parameters determined for each of the three daily doses in course 1 are summarized in Table III.

Higher maximum plasma concentrations ($C_{\max}$ mean, $124.8 \pm 26.8 \mu\text{g/L}$) and higher areas under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{last} , mean, $1071.1 \pm 231.7 \mu\text{g}\cdot\text{hr/L}$) were observed despite dose reduction in the two patients who received reduced pentostatin doses (patients #1 and #5) compared to patients receiving the standard dose (mean $C_{\max}$ and AUC_{last} $102.2 \pm 22.7 \mu\text{g/L}$ and $363.3 \pm 176.4 \mu\text{g}\cdot\text{hr/L}$, respectively). Plots of area under the extrapolated concentration-time curve from time zero to infinity normalized to dose ($\text{AUC}_{\infty\text{-D}}$) and pentostatin clearance versus eCR_{CL} are presented in figure 2(a) and 2(b), respectively. Plots of the maximum plasma concentration normalized to dose ($C_{\max\text{-D}}$) and versus creatinine clearance are presented in figure 2(c). The figures indicate that dose-normalized pentostatin exposures (i.e., $C_{\max}$ and AUC) are higher in patients with low eCrCL .

Patient #1 had an eCR_{CL} of $52.8 \text{ ml/min/1.73m}^2$, nonetheless decision was made to reduce dose by 50% because the patient's serum creatinine values had almost doubled from baseline. Unfortunately, despite dose reduction the patient's serum creatinine continued to rise and increased by another 0.6 mg/dL (from 1.77 to 2.37 mg/dL) on day 3. The patient was therefore removed from study after only 2 doses. Subsequent pharmacokinetic analyses reported a substantial AUC_{last} value of 838 and $1242 \mu\text{g}\cdot\text{hr/L}$ on days 1 and 2, respectively. Patient #5 was given the standard dose on days 1 and 2 per protocol based on eCR_{CL} of 59.3 and $61.4 \text{ ml/min/1.73m}^2$, respectively. Dose was reduced by 50% on day 3 due to an eCR_{CL} of $48.7 \text{ ml/min/1.73m}^2$. This patient also had significantly higher AUC_{last} values ($961 \mu\text{g}\cdot\text{hr/L}$ and $1347 \mu\text{g}\cdot\text{hr/L}$ after dose 1 and dose 2, respectively) compared to the other 6 patients who received full pentostatin doses. Despite dose reduction the AUC_{last} of this patient was determined to be $967 \mu\text{g}\cdot\text{hr/L}$, which is more than twice the average AUC_{last} of the patients who received 1.5 mg/m^2 of the drug ($363.3 \mu\text{g}\cdot\text{hr/L}$). The AUC_{∞} for the 3 doses at 0.75 mg/m^2 were estimated at 1346 , 8232 , and $1369 \mu\text{g}\cdot\text{hr/L}$; whereas the mean estimated AUC_{∞} for the 1.5 mg/m^2 doses was $591 \mu\text{g}\cdot\text{hr/L}$. Together, the data are consistent with earlier observations that patients with impaired renal function may exhibit reduced clearance and higher exposure to pentostatin.

The serum creatinine for patient #1 improved modestly on day 4 to 1.96 mg/dL . A 24-hr urine creatinine was collected to assess the patient's renal function on the same day. Despite a lower serum creatinine value, the measured creatinine clearance reported was $16.2 \text{ ml/min/1.73m}^2$.

4. Discussion

The estimated pharmacokinetic parameters reported here are similar to those previously reported for pentostatin,^[9,16,17] although AUC calculations appear slightly lower compared to the study by Bolanos-Meade et al.,^[9] who reported mean AUC_{∞} of $1,260 \pm 347 \mu\text{g}\cdot\text{hr/L}$ and $1,980 \pm 532 \mu\text{g}\cdot\text{hr/L}$ with a half-hour infusion of 1 mg/m^2 and 2 mg/m^2 , respectively. Altered pentostatin pharmacokinetics have been reported in patients with renal impairment,^[17] and data from the two patients in this study given reduced dose pentostatin

suggest that the standard recommended dose reduction may be inadequate and expose patients to high plasma concentrations of pentostatin with increased potential for severe adverse effects. No clear relationship is evident between response and pentostatin exposure (AUC) in this limited data set.

It should be noted that eCrCL values that were near the lower limit of the range (e.g., 50 ml/min/1.73m²) to receive a full pentostatin dose were observed in patient #7. The AUC values in these instances were comparable to those values observed in patients with higher eCrCL values, suggesting that 50 ml/min/1.73m² was an appropriate cutoff value for pentostatin dosing in patient #7. Notably, the 50% reduction in pentostatin dose that was employed in patients #1 and #5 was not sufficient to compensate for the reduced pentostatin clearance observed in these subjects. It is crucial to point out that the measured creatinine clearance from a 24-hr urine collection (16.2 ml/min/1.73m²) for patient #1 on day 4 was substantially lower than the eCrCL calculated using the Cockcroft-Gault equation (47.7 ml/min/1.73m²). A 24-hr urine was not collected from patient #5. This incident illustrated the pitfalls of utilizing the Cockcroft-Gault equation to estimate renal function of a critically ill patient. Examples of factors that could falsely decrease serum creatinine level include advanced-age, muscle wasting, malnutrition, poor performance status (limited mobility), *etc.*^[18] Similarly, estimated creatinine clearance has shown to be unreliable among patients with certain conditions such as, obesity or extreme body size, skeletal muscle disease, paraplegia/quadruplegia, vegetarian, rapidly changing kidney function, pregnancy, *etc.*^[19] The eCrCL should be interpreted with extreme cautions in these patients. Renal function assessment based on the Cockcroft-Gault method could be significantly overestimated and in this case pentostatin could be dosed inappropriately.

Patient #2, with persistent and severe cutaneous GVHD at trial entry and with the lowest pentostatin AUC in this study, achieved the single complete response observed. We presume that the lack of gastrointestinal and hepatic involvement combined with the minimal infectious complications allowed this patient to survive this episode of aGVHD. Additional data are required to determine if AUC is correlated with response as was seen in the phase I report with this dosing schedule.^[9]

5. Conclusion

Pentostatin use continues in the setting of chronic lymphocytic leukemia, hairy cell leukemia, chronic GVHD, and as part of the conditioning regimen for allogeneic stem cell transplantation. The data presented here imply that renal insufficiency plays a significant role in pentostatin exposure and patients with renal impairment who are critically ill may require further dose reduction than previously reported. A better understanding of the pharmacokinetics of pentostatin and the relationship of dose to immunosuppression could lead to improved outcomes with decreased infectious complications.

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Figure 1. Plasma pentostatin concentration versus time

Pentostatin concentrations were determined with an adenosine deaminase inhibition assay measuring the conversion of adenosine to inosine via UV absorbance. Plots are displayed for all patients and for all administered doses on the first 3 days of treatment.

Figure 2. (a) Dose-normalized plasma pentostatin AUC_{∞} versus estimated creatinine clearance
The outlier is from dose #2 from patient #1. **(b) Pentostatin clearance versus estimated creatinine clearance.** AUC_{∞} and clearance estimates were generated with non-compartmental analysis and normalized by dose. AUC_{∞} is the area under the plasma pentostatin concentration-time curve from time zero to infinity. **(c) Dose-normalized plasma pentostatin maximum concentration versus estimated creatinine clearance.** Creatinine clearance was estimated from serum creatinine measurements using the Cockcroft-Gault method. *Denotes dose on day 1, and ** dose on day 2 from patient #1, respectively.

Table 1

Demographics and transplant characteristics of study patients

ID	Age (y)	Disease	Donor & Matching	CMV D/R	Prep	GVHD Prophylaxis	ANC>500, PTD ^a	Plt > 20K, PTD ^a
1	49	Myeloproliferative disease	SIB 10/10	+/+	Bu/Cy	CSA/MTx ^b	+12	+18
2	22	Acute lymphocytic leukemia	URD 9/10	-/-	TBI/Cy	CSA/MTx ^b	+13	+49
3	53	Follicular lymphoma	SIB 6/6	+/-	Alentuzumab Fludarabine TBI ^c	FK/MMF ^d	+14	Never
4	34	Acute lymphocytic leukemia	SIB 10/10	+/+	TBI/VP	CSA/MTx ^b	+12	+19
5	61	Chronic lymphocytic leukemia	SIB 10/10	+/-	Alentuzumab Fludarabine TBI ^c	FK/MMF ^d	+24	+22
6	26	Acute myeloid leukemia	URD 9/10	+/+	Bu/Cy	CSA/MTx ^b	+14	Never
7	63	Chronic myelomonocytic leukemia	SIB 10/10	+/+	Bu/Cy	CSA/MTx ^b Infliximab ^e	+17	+26
8	47	Acute myeloid leukemia	URD 10/10	-/-	Bu/Cy	CSA/MTx ^b Infliximab ^e	+13	+18

^aPlatelet and neutrophil engraftment were defined as >20,000/mm³ and 500/mm³ respectively. Platelet engraftment never occurred in patients #3 and #6.

^bFor those patients receiving cyclosporine, they received 3 mg/kg/day intravenous commencing on day -1 and short-course methotrexate 15 mg/m² day 1 and 10 mg/m² days 3, 6, and 11.

^cFor patients #3 and #5, the preparative regimen consisted of Alentuzumab 20 mg IV days -4 & -3, Fludarabine 30 mg/m² IV days -4, -3, -2, and TBI 200 cGy on day -1.

^dFor those patients receiving tacrolimus with methotrexate, they received 0.03 mg/kg/day intravenously commencing on day -2.

^eFor patients #7 and #8, infliximab was administered as a 120-minute infusion at 10 mg/kg the day before the conditioning regimen as part of a clinical trial investigating infliximab's activity in GVHD prophylaxis; five subsequent doses were given on days 0, 17, 114, 128, and 142.

Abbreviations ANC=Absolute neutrophil counts; Bu=Busulfan; CMV=Cytomegalovirus; CSA=Cyclosporine; Cy=Cyclophosphamide; DLI=Donor lymphocyte infusion; D/R=Donor/Recipient status; FK=Tacrolimus; GVHD=Graft-versus-host disease; MMF=Mycophenolate mofetil; MTx=Methotrexate; Plt=Platelets; Prep = preparative regimen; PTD=Post-transplant day; SIB=Sibling; TBI=Total body irradiation; URD=Unrelated donor; VP=Etoposide.

Table II

Clinical course of study subjects

ID	DLI	GVHD Dx PTD	GVHD Grade at Dx	Involved Organs	Pentostatin start PTD	GVHD Response	Therapy related Complications	Death, PTD	COD
1	--	+16	4	Skin, gut, liver	+25	Mixed	CMV viremia	+42	GVHD
2	--	+11	4	Skin	+24	CR	CMV viremia	Alive	
3	+68	+85	4	Skin, gut, liver	+103	PD	CMV viremia	+130	Sepsis
4	+68	+103	2	Skin, liver	+114	PD		+147	GVHD
5	--	+17	4	Skin, gut	+51	N/E	CMV viremia, sepsis	+56	Sepsis
6	--	+8	3	Skin, gut	+27	PD	CMV viremia, Pneumonia	+48	Sepsis
7	--	+24	3	Skin, gut, liver	+31	Mixed	CMV viremia	+56	GVHD
8	--	+15	3	Gut, liver	+20	Mixed	CMV viremia	+51	GVHD

COD (cause of death) was listed as GVHD if the patient had progressive GVHD when the patient expired. GVHD grading was defined using modified Keystone Acute GVHD grading criteria. Patients ID #1, 7, and 8 all responded with skin and/or gut GVHD but hepatic GVHD did not respond.

Abbreviations: CMV=Cytomegalovirus; CR=Complete response; DLI=Donor lymphocyte infusion; Dx=Diagnosis; N/E=Non-evaluable; PD=Progression of disease; PTD=Post-transplant day;

Table III

Non-compartmental pharmacokinetic parameter estimates

Patient ID	1		2		3		4		5		6		7		8								
Treatment Day	1	2	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3						
t _{1/2} (h)	12.2	107.92	2.44	0.49	0.75	3.25	7.28	7.87	13.11	3.06	2.21	10.91	15.76	14.51	3.94	3.87	7.53	6.85	10.55	12.59	1.8	4.47	1.76
t _{max} (h)	0.58	0.67	0.58	0.58	0.72	0.67	0.67	0.58	0.67	0.58	0.58	0.42	0.58	0.82	0.5	0.58	0.58	0.77	0.58	2.5	0.62	0.6	0.58
C _{max} (µg/L)	156	145	105	102	70	116	76	109	134	132	99	106	126	91	114	114	114	94	108	46	76	113	106
t _{last} (h)	24.33	24.5	8.5	2.5	2.63	8.5	24.5	8.5	24.53	8.58	8.5	24.33	25.5	24.58	8.42	24.03	8.47	24.1	21.3	24.48	8.67	8.65	8.52
AUC _{last} (µg•h/L)	838	1242	274	124	106	284	480	327	496	347	214	961	1347	967	548	528	553	477	530	687	159	204	201
AUC _∞ (µg•h/L)	1346	8232	304	129	119	373	525	582	613	439	246	1203	1979	1369	676	536	1160	512	683	935	174	251	219
V _z (L/m ²)	9.80	14.20	17.40	8.30	13.60	18.80	30.00	29.30	46.30	15.10	19.40	19.60	17.20	11.50	12.60	15.60	14.10	28.90	33.40	29.20	22.30	38.50	17.30
CL (L/h/m ²)	0.60	0.10	4.90	11.70	12.60	4.00	2.90	2.60	2.40	3.40	6.10	1.20	0.80	0.50	2.20	2.80	1.30	2.90	2.20	1.60	8.60	6.00	6.80
eCL _{CR} (mL/min/1.73m ²)	52.8	52.8	102.9	126.3	111.1	89.9	93.7	89.0	135.8	106.2	111.3	59.3	61.4	48.7	119.5	111.3	112.4	57.9	66.8	65.7	79.1	85.2	101.7
Pentostatin dose (mg/m ²)	0.75 ^a	0.75 ^a	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	0.75 ^a	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50

Individual pharmacokinetic parameter estimates are listed for each patient and each day of treatment on course 1. Non-compartmental parameter estimates were generated after excluding concentrations below measurable levels. Data points for determining the terminal elimination phase (λ_z) were selected automatically in WinNonlin and resulting λ_z ranges were determined to be adequate by manual review. A total of 23 doses were administered during course 1 (one patient did not receive the 3rd dose) providing 146 plasma samples for pentostatin concentration determination and 23 concentration-time profiles. Pentostatin concentrations were below measurable limits for 22 of the plasma samples evaluated.

^aReduced doses of 0.75 mg/m²

Abbreviations: AUC_{last}=Area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_∞=Area under the plasma concentration-time curve from time zero to infinity; CL=Apparent total body clearance of the drug from plasma; eCL_{CR}=Cockcroft-Gault estimated creatinine clearance; C_{max}=Maximum observed plasma concentration; t_{max}=Time to reach C_{max}; t_{1/2}=Elimination half-life determined from the terminal elimination phase; t_{last}=Time of the last observed plasma concentration. V_z=Apparent volume of distribution during terminal phase is volume of distribution.