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Pharmacokinetics and toxicity of 120-hour continuous-infusion hydroxyurea in patients with advanced solid tumors

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Abstract A group of 18 patients with advanced cancer were entered on a phase I study of a 120-h continuous intravenous infusion of hydroxyurea. The dose of hydroxyurea was escalated in cohorts of patients from 1 to 2 to 3.2 g/m^2 per day. The primary dose-limiting toxicity was neutropenia, often accompanied by leukopenia, thrombocytopenia and generalized skin rash. Prophylactic treatment of patients with dexamethasone and diphenhydramine hydrochloride prevented the skin rash, but not the hematopoietic toxicities. The pharmacokinetics of hydroxyurea were studied in all patients. The steady-state concentrations of hydroxyurea were linearly correlated with the dose (R^2 = 0.71, n = 18, $P < 0.0001$). The mean ± SE concentrations were 93 ± 16, 230 ± 6 and 302 ± 27 μ*M* at 1, 2 and 3.2 g/m^2 per day, respectively. The mean ± SE renal and nonrenal clearances of hydroxyurea were 2.14 ± 0.18 and 3.39 ± 0.28 l/h per m^2 (n = 16), neither of which correlated with the dose. The concentration of hydroxyurea in plasma decayed monoexponentially with a mean ± SE half-life of 3.25 ± 0.18 h (n = 17). The steady-state concentration of hydroxyurea was > 200 μ*M* in all nine patients treated at 2 g/m^2 per day, a dose which was well tolerated for 5 days. We recommend this dose for phase II trials in combination with other antineoplastic agents.

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Abbreviations *ANC* absolute neutrophil count · CL_{cr} creatinine clearance · CL_{nr} nonreal clearance · CL_p plasma clearance · CL_r renal clearance · C_p plasma concentration · C_{ss} steady state concentration · *CT* computerized tomogram · *DHFR* dihydrofolate reductase · *IV* intravenous · $t_{1/2}$ half-life.

Introduction

Hydroxyurea is an S-phase selective inhibitor of ribonucleotide reductase. Its mechanism of action, activity in preclinical studies, and clinical use have been reviewed by Moore and Hurlbert [11]. Although most often used to treat chronic myelogenous leukemia, hydroxyurea has been used experimentally to treat other malignancies and a few nonmalignant disorders. It has been used both as a single agent and in combination with several other antineoplastic drugs. Because hydroxyurea inhibits the *de novo* synthesis of deoxynucleoside diphosphates, rational combinations have included hydroxyurea with antimetabolites which compete with deoxynucleotides at their sites of action. Examples of the latter include 5-fluorouracil [12, 13], 1-β-D-arabinofuranosylcytosine [8, 15], and more recently dideoxynucleosides [2, 7, 9]. Hydroxyurea also inhibits DNA repair, suggesting its use with DNA damaging agents, including cisplatin, etoposide and radiation [20]. Hydroxyurea at a concentration of 50 μ*M* has also been shown to accelerate the loss of extrachromosomally amplified dihydrofolate reductase (DHFR) genes [17]. These results have been confirmed with regard to the loss of DHFR from methotrexate-resistant cells, and extended to the loss of the multidrug resistance gene (MDR1) from vinblastine-resistant cells and to the loss of carbamylphosphate synthetase, aspartate transcarbamylase and dihydroorotase genes from *N*-(phosphonacetyl)-L-aspartic acid-resistant cells. In each case, continuous exposure to concentrations of hydroxyurea

between 50 and 200 μ*M* accelerates the loss of the extrachromosomally amplified elements, but requires multiple cell doublings (several days) to reduce the copy number by 50% [4, 19]. The number of doublings required decreases as the concentration of hydroxyurea increases [19]. Likewise, hydroxyurea accelerates the loss of extrachromosomally amplified c-myc and induces differentiation in HL60 cells [5].

The toxicity and pharmacokinetics of hydroxyurea administered by both frequent oral administration (every 4 h for 18 doses) and continuous intravenous (IV) infusion for 72 h have been described [1]. The peak concentration of hydroxyurea in patients treated with the same oral dose varies by two- to threefold; the time to the peak concentration varies by as much as fourfold. Administered by continuous IV infusion at the maximum tolerated rate of 3.0 mg/m^2 per min (4.32 g/m^2 per day) for 72 h, a steady-state level of 1 m*M* hydroxyurea is obtained within 24 h. The postinfusion $t_{1/2}$ is approximately 4 h. In a study of 5-fluorodeoxyuridine combined with high-dose leucovorin and oral hydroxyurea, we have found mucositis and diarrhea to be the dose-limiting toxicities [14]. Preliminary pharmacokinetic data from three patients on that study indicate a twofold range in the peak plasma concentrations of hydroxyurea (unpublished data). It is possible, however, that the gastrointestinal toxicity of the chemotherapy regimen contributed to the variability in hydroxyurea bioavailability. This potential for variable absorption led us to examine the continuous IV administration of hydroxyurea for 120 h, a schedule which could be combined with daily administration of a fluoropyrimidine for 5 days. The lengthened time of exposure to hydroxyurea might also be more appropriate to reduce the copy number of extrachromosomally amplified genes.

Materials and methods

Patient eligibility

All patients entered on this study had histologically proven cancer which was metastatic or locally unmanageable by conventional therapy, a Karnofsky performance status of 60% or better, and an estimated survival of at least 8 weeks. They also had adequate bone marrow function (hemoglobin $\geq$10 g/dl, ANC $\geq$3000/μl, platelet count $\geq$150 000/μl), hepatic function (total bilirubin $<$1.6 mg/dl, serum transaminases less than four times the upper limit of normal) and renal function (serum creatinine $\leq$1.6 mg/dl or CL_{cr} $\geq$50 ml/min). No restrictions were placed on prior radiotherapy or chemotherapy if completed at least 4 weeks before study entry. Pregnant women were excluded. An exception to the standard entry criteria was granted for one patient whose hemoglobin at study entry was 9.3 g/dl. All patients were over 18 years of age and signed informed consent in accord with federal, state, and local guidelines.

Pretreatment and safety evaluations

Before initiation of chemotherapy, all patients underwent a complete history and physical examination. Laboratory studies included a complete blood count, a platelet count, an 18-function blood chemistry profile and Mg^{++} level, a urinalysis and an electrocardiogram. A chest radiograph, a bone scan or a liver CT were obtained only if clinically indicated or required for measurement of a lesion. The complete blood count, platelet count, and blood chemistries were repeated weekly; the history and physical examination, CL_{cr}, urinalysis and radiographs or scans needed for measurement of a lesion, prior to each treatment cycle. (Measurements necessitating a CT were required only every two cycles unless there were signs or symptoms of progression.) Laboratory and clinical assessments were carried out more frequently if clinically warranted. Laboratory values exhibiting clinically significant changes were repeated until they returned to normal, returned to pretreatment values or stabilized. Toxicities were graded using the Common Toxicity Scale of the National Cancer Institute.

Study design and treatment plan

Hydroxyurea was administered by continuous IV infusion over 120 h. Patients were admitted to the hospital for treatment cycles, which were repeated every 21 days. The initial dose of hydroxyurea was 1 g/m^2 per day. The dose was escalated in cohorts of patients following a modified Fibonacci pattern to 2 g/m^2 per day and then to 3.2 g/m^2 per day. Escalation of the dose of hydroxyurea for a given patient was not allowed. Patients who experienced a grade 4 nonhematologic toxicity were removed from protocol therapy. Patients who experienced a grade 3 nonhematologic toxicity were retreated at a dosage reduction of one level. Escalation of the dose of hydroxyurea for cohorts of patients was based on the toxicities in the first cycle of treatment. A minimum of three patients were entered at each dose level. If no grade 3 or 4 toxicity was observed in the three patients, the dose was escalated one level. If a single patient had grade 3 toxicity, three additional patients were treated at the same dose level before escalation. The maximum tolerated dose was defined as the dose at which two patients had grade 3 or one patient had grade 4 toxicity. At least six patients were treated at one dose level below the maximum tolerated dose. When generalized skin rash was encountered at 3.2 g/m^2 per day, the protocol was amended to administer oral dexamethasone (2 mg) and diphenhydramine hydrochloride (25 mg) before the start of the hydroxyurea infusion and every 6 h until the patient was discharged. A cohort of six patients were treated at the prior dose level (2 g/m^2 per day) before attempting to re-escalate the dose of hydroxyurea.

Evaluation of toxicity and efficacy

All patients completed at least one cycle of protocol therapy and were evaluable for toxicity. Efficacy was determined in patients with bidimensionally measurable lesions. Complete response was defined as the disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. Partial response was defined as a decrease of $\geq$50% in the sum of the products of the diameters of the measurable lesion(s), without evidence of new lesions for two consecutive evaluations separated by at least 4 weeks. The same criteria were used whether single or multiple lesions were evaluated. Disease progression was defined as an increase of $\geq$25% in the area of the measurable lesion(s) over the size at maximum regression or the appearance of new lesions. Disease not meeting these criteria for response or progression was considered stable. All patient evaluations were performed by at least one member of the Department of Biostatistics and one of the authors.

Pharmacokinetics

Plasma samples were obtained daily during the infusion, with the first sample obtained at least 12 h after the beginning of the infusion. After the end of the infusion, plasma was obtained every 2 h for 12 h. Urine was collected during a 24-h period, beginning and ending at the time of the daily plasma sampling. C_{ss} values were estimated as the means of samples from each patient obtained during the infusion. Clearances were calculated in individual patients at steady state using the following equations: CL_p = dose rate/C_{ss}; CL_r = amount excreted/($C_p \times 24$ h); $CL_{nr} = CL_p - CL_r$. Clearances were normalized based on each patient's body surface area. The $t_{1/2}$ half-life of hydroxyurea in each patient was estimated by a least-squares fit of the postinfusion C_p to a single exponential decay.

Table 1 Patient characteristics

Characteristic	No. of patients
Patients entered	18
Age (years)	
Mean	58
Range	38–68
Gender	
Women	10
Men	8
Karnofsky performance status	
60%	1
70%	2
80%	5
90%	8
100%	2
Prior therapy	
Surgery	12
Radiotherapy	9
Chemotherapy	15
No. of prior regimens	
0	3
1	5
2	6
≥3	4

Analytical methods

Hydroxyurea was assayed by the colorimetric method of Fabricius and Rajewsky [6]. However, plasma samples were diluted only 1:2 with water prior to perchloric acid deproteination and required less sodium hydroxide to adjust the pH to between 6.9 and 7.3 than was reported for samples diluted 1:10. (The pH is critical for stable color development in the assay.) Urine samples were diluted 1:100 with water prior to the addition of perchloric acid.

Statistical methods

Unless otherwise indicated, data are presented as means ±SE. Correlations between pairs of variables were determined by linear regressions. The means of parameter values were compared by independent *t*-tests. Significance was tested at the 0.05 level using two-sided *P*-values.

Results

Patient characteristics

Of 18 patients entered on this study, there were 6 with colorectal cancer (33%), 4 with lung cancer (22%), and 1 each with primary disease at eight other sites. The demographic features of the patients are shown in Table 1. Of the 18 patients, 12 had prior surgical resections, 9 had prior radiotherapy, 3 had no prior chemotherapy (1 with hepatocellular carcinoma, 1 with adenocarcinoma of the pancreas, and 1 with adenocarcinoma of unknown primary origin), 1 had received only adjuvant chemotherapy, 2 had received chemotherapy only for their primary disease, and 12 had received one or more courses of chemotherapy for metastatic disease (4 of whom had also received adjuvant chemotherapy).

Table 2 Toxicity of first cycle of hydroxyurea

		Hydroxyurea dose (gm/m²/day)×5 days				
					With dexamethasone and diphenhydramine	
Toxicity	Grade	1.0	2.0	3.2	2.0	3.2
ANC/nl						
0.5–0.9	3	0	0	1	0	0
<0.5	4	0	0	2	0	2
WBC/nl						
1.0–1.9	3	0	0	1	0	0
<1.0	4	0	0	1	0	1
Platelets/nl						
25.0–49.9	3	0	0	0	0	1
Skin rash						
Generalized symptomatic	3	0	0	2	0	0

Toxicity

All toxicities for which there was at least one drug-related occurrence graded 3 or higher are listed in Table 2. No toxicities of more than grade 2 were observed at doses of 1 or 2 g/m² per day. A dose of 3.2 g/m² per day of hydroxyurea, without dexamethasone and diphenhydramine hydrochloride, produced grade 4 neutropenia in two patients and grade 3 in one patient. In the two patients with grade 4 neutropenia, the ANCs were <500/μl for 6 and 12 days. The nadirs occurred 8 and 10 days from the start of therapy. The grade 4 neutropenia was accompanied by grade 3 or 4 leukopenia and grade 3 generalized skin rash. The grade 3 neutropenia was accompanied by grade 2 leukopenia and grade 2 skin rash.

Treatment with dexamethasone and diphenhydramine hydrochloride protected against the skin rash, but not the hematopoietic toxicity of 3.2 g/m² per day of hydroxyurea. Two of three patients at this dose experienced grade 4 neutropenia. The ANCs were <500/μl for 6 and 7 days. The nadirs occurred 10 and 15 days from the start of therapy. In one patient, neutropenia was accompanied by grade 4 leukopenia and grade 3 thrombocytopenia and in the other patient, by grade 2 leukopenia.

Extent of treatment and response to therapy

The number of cycles administered to each cohort of patients is listed in Table 3. All of the patients treated with 2 g/m² per day of hydroxyurea, with or without dexamethasone and diphenhydramine hydrochloride, received multiple cycles of therapy on protocol without dose reductions. Four patients received two cycles, 1 three cycles, 2 four cycles, 1 five cycles and 1 six cycles.

One patient treated with 3.2 g/m² per day of hydroxyurea without dexamethasone and diphenhydramine hydrochloride withdrew from the study after a single cycle of chemotherapy and was not evaluable for response. There were no objective responses in the 17 evaluable patients.

Table 3 Number of cycles of hydroxyurea administered

	Hydroxyurea dose (gm/m²/day)×5 days					
					With dexamethasone and diphenhydramine	
	Total	1.0	2.0	3.2	2.0	3.2
Patients	18	3	3	3	6	3
Cycles	52	7	10	6	20	9

Pharmacokinetics

The pharmacokinetic parameters are summarized by dose in Table 4. The C_{ss} values of hydroxyurea were linearly correlated with the dose (Fig. 1, $R^2 = 0.71$, $n = 18$, $P < 0.0001$). As expected from the linear relationship between the dose and the C_{ss}, the CL_r, the CL_{nr} and the $t_{1/2}$ did not correlate with the dose. The means of the dose-independent pharmacokinetic parameters were not significantly different with and without coadministration of dexamethasone and diphenhydramine hydrochloride. Figure 2 illustrates the combined postinfusion data for all patients who received 2 g/m² per day of hydroxyurea. The data with and without dexamethasone and diphenhydramine hydrochloride are shown by open and closed symbols, respectively. A regression line for the logarithmic fit to the combined data is included for illustration although the mean $t_{1/2}$ values in Table 4 were obtained by fitting the data individually for each patient and subsequently averaging the results.

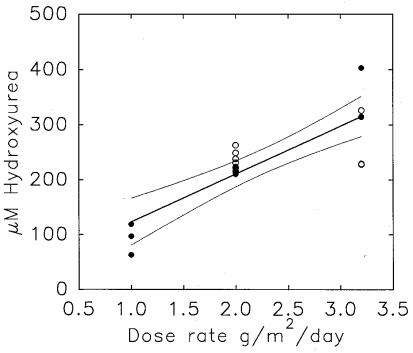

Fig. 1 Steady-state plasma concentrations of hydroxyurea as a function of the dose rate. The *solid symbols* represent data from patients who did not receive dexamethasone and diphenhydramine hydrochloride and the *open symbols*, data from patients who did. The linear regression line is shown together with the 95% confidence interval

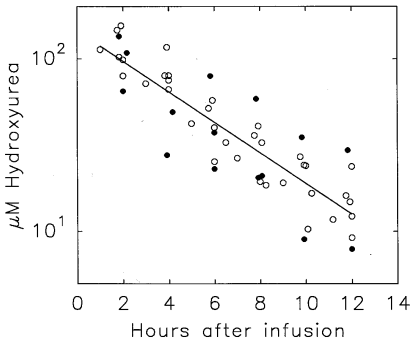

Fig. 2 Plasma concentrations of hydroxyurea as a function of time after a 120-h infusion at 2 g/m² per day. The symbols are as in Fig. 1. The logarithmic regression line for the combined data is shown

Discussion

Neutropenia was the dose-limiting toxicity of hydroxyurea administered by 120-h continuous IV infusion. This is consistent with the reported toxicity of a 72-h infusion [1]. Although myelosuppression was grade 4 by the National Cancer Institute common toxicity criterion of an ANC nadir $< 500/\mu l$, it resolved quickly within 6 to 12 days. Belt et al. [1] have hypothesized that the duration of infusion might be extended beyond 72 h without increasing significantly the degree of myelosuppression. However, both our data and previously reported data for continuous IV infusions of hydroxyurea lasting between 1 and 12 weeks [3] indicate that myelosuppression increases with increasing duration of administration. Therefore, only lower dose rates were tolerated at the longer durations.

Extensive dermatologic reactions were observed in this study when dexamethasone and diphenhydramine hydrochloride were not administered prophylactically. This is a less-common side effect of hydroxyurea, but has been reported with long-term daily hydroxyurea therapy [10]. The high frequency of generalized symptomatic skin rash

Table 4 Pharmacokinetic parameters. Values are means ± SE with the number of observations in parentheses

Hydroxyurea dose (g/m²/day)	C_{ss} (μ*M*)	CL_p (l/h/m²)	CL_r (l/h/m²)	CL_{nr} (l/h/m²)	$t_{1/2}$ (h)
1.0	93±16 (3)	6.3±1.2 (3)	2.7±0.1 (3)	3.6±1.3 (3)	2.8±0.2 (3)
2.0	230± 6 (9)	4.8±0.1 (9)	1.8±0.2 (9)	3.0±0.2 (9)	3.2±0.2 (9)
3.2	302±27 (6)	6.0±0.5 (6)	2.6±0.4 (4)	4.0±0.4 (4)	3.7±0.4 (5)
All		5.5±0.3 (18)	2.1±0.2 (16)	3.4±0.3 (16)	3.3±0.2 (17)

appears to be unique to the 120-h schedule because it has not been noted at higher dose rates for shorter durations [1, 16] nor at lower dose rates for longer durations [3]. However, stomatitis has been reported to be a "surprising" dose-limiting side effect of long-term continuous IV infusions of hydroxyurea [3].

New potential therapeutic uses for hydroxyurea have generated a renewed interest in its pharmacokinetics following administration in a variety of schedules. In addition to the study of 120-h continuous IV infusion reported here, recent reports have described the pharmacokinetics of hydroxyurea administered by long-term IV infusion (1 to 12 weeks) [3] and by high-dose continuous IV infusions (24 to 72 h) [16, 18]. Our results were consistent with linear pharmacokinetics over the dosage range studied (1 to 3.2 g/m^2 per day). Nonlinear pharmacokinetics have been reported for hydroxyurea over a range of dose rates from 2 to 14.4 g/m^2 per day [18]. Because higher dose rates of hydroxyurea are not tolerated for 120 h, the C_p values do not appear to be high enough for saturation of the metabolic component of the proposed nonlinear model to be evident. The C_{ss} value at a dose rate of 3.2 g/m^2 per day was 302 μ*M* in this study, whereas the reported K_M for the nonlinear model is 323 μ*M* [18].

The dose rate and duration of hydroxyurea to be used in future clinical trials will depend on several factors. The duration in protocols using hydroxyurea to modulate the activity of other agents will depend on the schedule of administration of the agents with which hydroxyurea is combined. The duration in protocols intended to induce the loss of extrachromosomal elements will need to be carefully considered. Although 200 μ*M* hydroxyurea produces a more rapid loss of such elements than does 50 μ*M* in vitro, 50 μ*M* is sufficient to induce the loss over time [19], and plasma levels of approximately 50 μ*M* can be safely maintained indefinitely [3]. When used to reverse resistance to other drugs, the toxicity of the hydroxyurea must be balanced against the delay in administering the other drug. When the loss of the extrachromosomal element is hypothesized to be of direct therapeutic benefit (see, for example, reference 5), then the toxicity must be balanced against the growth rate of the tumor. The infusion duration of 120 h used in this study was chosen principally to facilitate the development of future protocols combining continuous-infusion hydroxyurea with a fluoropyrimidine administered daily for 5 days. The dose rate of 2 g/m^2 per day was well tolerated for 5 days and resulted in a C_{ss} of hydroxyurea >200 μ*M* in all nine patients treated. This dose would be appropriate in phase II trials either for biochemical modulation of other antineoplastic agents or to diminish drug resistance mediated by extrachromosomally amplified genetic material within a few cell generations.

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