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A Phase I and pharmacokinetics study of 2-chlorodeoxyadenosine in patients with solid tumors

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Abstract Preclinical studies of 2-chlorodeoxyadenosine (2-CdA) against solid tumors in the human tumor cloning assay and evidence that 2-CdA is active against slow-growing or resting tumor cells have stimulated interest in the clinical activity of this agent against solid tumors. This study sought to estimate the maximum tolerated dose, dose-limiting toxicity, and plasma and urine pharmacokinetics accompanying the intravenous administration of 2-CdA by 120-h continuous infusion in patients with solid tumors. Treated patients were also assessed for other toxicities of therapy and for antitumor response. A total of 23 patients received 35 courses of treatment given at doses of 3.5, 5.3, 6.5 and 8.1 mg/m^2 per day by continuous intravenous infusion for 5 days and repeated every 28 days. Blood and urine specimens were collected before, during, and after drug infusion. The dose-limiting toxicity at 8.1 mg/m^2 per day manifested as granulocytopenia in 2 of 5 patients (3 of 7 courses of treatment) and as thrombocytopenia in 3 of 5 patients (3 of 7 courses of treatment). At the dose levels of 6.5 and 8.1 mg/m^2 per day, recovery from thrombocytopenia was often delayed. Severe lymphocytopenia ($< 1{,}000/\mu l$) was observed at all dose levels of 2-CdA. Dose-related anemia and leukopenia were observed and were infrequently severe. Nonhematological toxicities were confined to mild-to-moderate nausea, vomiting, fatigue, and anorexia. Fever of 37°–40°C was induced during drug infusion in 19 patients. No antitumor response was observed. Average plasma concentrations at steady-state (Cp_{ss}) ranged from 3 ng/ml at the initial dose level to 13 ng/ml at the dose level of 8.1 mg/m^2 per day. Both the Cp_{ss} and the area under the plasma concentration-time curve (AUC) were proportional to the dose. A relationship was observed between the percentage of change in absolute neutrophil count and the AUC. Renal excretion accounted for only 18% of the elimination of 2-CdA over the 5-day infusion period. The maximum tolerated dose for 2-CdA given by 5-day continuous infusion was 8.1 mg/m^2 per day in this study. The recommended dose on this schedule for phase II studies is 6.5 mg/m^2 per day. Granulocytopenia and thrombocytopenia were dose-limiting. No antitumor activity was observed during this study. On the basis of the plasma concentrations of 2-CdA observed, it is unlikely that this schedule of drug administration will permit achievement of the concentrations consistent with antitumor activity observed in preclinical studies.

Key words 2-chlorodeoxyadenosine · Phase I · Pharmacokinetics · Solid tumors

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Introduction

Synthetic analogues of adenine have assumed important roles in the management of various lymphoreticular malignancies in man. Fludarabine phosphate, the first adenine analogue to enter clinical trials for the treatment of chronic lymphocytic leukemia, induced remissions in a high proportion of patients afflicted with this malignancy [2, 3, 9]. 2-Chlorodeoxyadenosine (2-CdA; cladribine; NSC-105014) was the second adenine analogue subjected to clinical investigation for

lymphoreticular malignancies. Like fludarabine phosphate, 2-CdA is halogenated at the 2 position of the adenine ring, rendering the compound resistant to degradation by adenosine deaminase, an enzyme found ubiquitously in human tissues and at high activity in lymphoid cells. 2-CdA is converted to 2-chlorodeoxyadenosine monophosphate by deoxycytidine kinase, also found at high levels of activity in lymphoid cells. The triphosphate product may be incorporated into DNA, can cause single-strand breaks in DNA, may inhibit DNA repair, can cause allosteric block of ribonucleotide reductase and thereby impair the production of deoxynucleotide, and may inhibit DNA-chain elongation. Nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP) are depleted and eventuate in cell death [1]. Unlike other nucleoside analogues, 2-CdA is effective in resting lymphoid cells [18].

2-CdA is active against hairy-cell leukemia, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia (4, 6–8, 12, 13, 15–17, 19). Durable remissions in patients with hairy cell leukemia have been induced at a dose of 0.1 mg/kg per day by 7-day continuous intravenous infusion. Like fludarabine phosphate, 2-CdA is capable of inducing complete remissions in a small proportion of patients with chronic lymphocytic leukemia. Indeed, 2-CdA does not appear to be cross-resistant with fludarabine phosphate, despite the two agents' structural similarity [7]. In phase I and phase II clinical trials, the toxicities of 2-CdA have been fairly well-defined and appear dose-related. In all studies, the predominant toxicity has been myelosuppression (neutropenia, thrombocytopenia, anemia, and lymphocytopenia).

Interest in the clinical use of 2-CdA against human solid tumors has been based upon the drug's resistance to adenosine deaminase, evidence for its activity against slow growing malignancies, and preclinical evidence of activity against a variety of solid tumors in the human tumor cloning assay. Hutton and Von Hoff [5] demonstrated in vitro activity of 2-CdA against renal-cell carcinoma, non-small–cell lung carcinoma, ovarian carcinoma, and breast cancer. The agent was active against a greater number of tumors with continuous exposure to the drug than with 1-h exposure. Antitumor activity was seen at concentrations of 1.0 and 10 μg/ml, and little concentration-dependent difference in activity was discerned. This report describes a phase I trial of 2-CdA given by 5-day continuous intravenous infusion to patients with refractory solid malignancies.

Materials and methods

Patient selection

Eligible patients were those who had histologically confirmed, advanced solid cancers resistant to all known effective therapies and for whom curative treatment did not exist. Patients were 18 years of age or older, had an estimated life expectancy of 6 weeks or better, and had a Southwest Oncology Group performance status of 3 or less. All patients manifested evidence of adequate organ function (neutrophils, $\geq$ 1,500/μl; hemoglobin, $\geq$ 10 g/dl; platelet count, $\geq$ 100,000/μl; serum bilirubin, $\leq$ 2.0 mg/dl; serum creatinine, $\leq$ 2.0 mg/dl). Eligible patients must have recovered from toxicities of prior therapy and must not have received any anticancer therapy within 4 weeks of the onset of treatment with 2-CdA. All patients provided written evidence of informed consent consistent with federal and institutional guidelines.

Treatment plan

Prior to therapy, all patients had a complete medical history taken and underwent a physical examination. Baseline diagnostic studies included a complete blood count, differential count, and platelet count; determinations of serum bilirubin, serum creatinine, prothrombin time, and partial thromboplastin time, a urinalysis, a two-view chest X-ray; and an electrocardiogram. Pretreatment radiology studies were obtained for those patients with measurable or evaluable evidence of cancer.

2-CdA was supplied by the Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute as a 1-mg/ml sterile solution in 0.9% Sodium Chloride for Injection, USP. The desired 24-h dose was added to 100–500 ml 0.9% NaCl and was infused through a peripheral vein or through a central venous catheter using a volumetric pump. 2-CdA was freshly prepared each day for the succeeding 24-h infusion.

The starting dose of 2-CdA, 3.5 mg/m^2 per day, given by continuous intravenous infusion for 5 days was chosen on the basis of prior phase I and phase II trials of 2-CdA given over 7 days for the treatment of hematological and lymphoreticular malignancies. At least 3 patients were treated at each dose level and must have experienced tolerable toxicity before the enrollment of new patients to higher dose levels was permitted. After the starting dose, escalation of the dose occurred stepwise to 5.3, 6.5, and then 8.1 mg/m^2 per day. Intrapatient dose escalation was permitted only after 3 new patients had been treated and observed at the next higher dose level. Courses of treatment were repeated every 28 days if all toxicity of the prior course of therapy had resolved.

Following each 5-day course of treatment, patients returned at weekly intervals for follow-up examination, which included a toxicity query, physical examination, complete blood count, differential count, and platelet count, and determinations of serum creatinine and serum bilirubin; blood sampling for lymphocyte count; and a urinalysis. All baseline diagnostic and laboratory studies were repeated immediately before the next planned course of treatment. Radiology studies for tumor assessment were repeated after two courses of treatment. The first patient treated at each dose level was observed for 2 weeks for the emergence of significant clinical toxicity before additional patients were treated at that dose level. If grade 3 or greater toxicity (NCI Common Toxicity Criteria) was observed in 1 or more patients at a given dose level, an additional 3 patients were entered at that dose level before escalation to the next level occurred. The maximum tolerated dose was defined as that dose at which 2 or more patients experienced grade 3 or greater nonhematological toxicity or grade 4 hematological toxicity. If severe or life-threatening toxicity was observed in any patient, that patient was retreated at the next lower dose level. Patients were removed from study if unacceptable toxicity was observed, if the patient's cancer progressed, or if the patient refused further therapy.

For those patients with measurable disease, standard response criteria were utilized. A complete response was defined as the complete disappearance of all clinical evidence of cancer for at least

1 month and the absence of new lesions. A partial response was defined as a $\geq$ 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions as compared with the baseline value for at least 1 month. Progressive disease was defined as a $\geq$ 25% increase in the sum of the areas of all measurable lesions. Stable disease was defined as that evidence of disease not meeting the criteria for a complete or partial response or progressive disease.

Pharmacokinetic analysis

Blood specimens for pharmacokinetic studies were obtained from 17 of the 23 patients receiving 2-CdA during the first cycle of therapy. Heparinized blood samples were obtained prestudy, at 12, 36, 60, 84, and 108 h during the infusion; and at the end of the infusion. Additional samples were obtained postinfusion at 5, 10, 30, and 60 min and at 2, 3, 4, 6, 8, 12, 16, 24, and 36 h. Plasma concentrations of 2-CdA were obtained by a modified high-performance liquid chromatography (HPLC) assay previously described by Liliemark and Juliusson [10]. The major modifications to the assay included (1) extraction of the plasma sample twice with ethylacetate (increasing our recovery of 2-CdA to 95%), and (2) reextraction of the evaporated, reconstituted sample with chloroform to remove interfering substances. The lower limit of sensitivity for this assay was 2 ng/ml (twice the baseline noise level), and the weighted standard curves were linear ($r^2 = 0.996$) over the range of 2–100 ng/ml. The 2-CdA analytical reference standard was obtained from the Pharmaceutical Management Branch, Division of Cancer Treatment, National Cancer Institute. An HPLC assay for the detection of 2-CdA in urine was developed. Briefly, 1 ml urine was extracted twice with 5 ml ethylacetate, evaporated to dryness, and redissolved in the mobile phase. The stationary phase consisted of a Waters C_{18} column (μ Bondapak, 10μm, 3.9 × 300 mm; Waters Associates, Milford, Mass). The mobile phase was a mixture of 5% ethanol and 95% of a solution of 10 mmol sodium phosphate buffer (pH 4.0) pumped at a rate of 2 ml/min (Model 510 pump, Waters Associates). UV detection was accomplished at a wavelength of 265 nm (Model 486, Waters Associates). Standard curves constructed in non-treated donor urine were linear ($r^2 = 0.999$) from 0.1 to 4.0 μg/ml.

Results

Patients characteristics

The patients' characteristics are summarized in Table 1. A total of 23 patients were enrolled in this phase I trial and received 35 courses of treatment given at doses ranging from 3.5 to 8.1 mg/m^2 per day (median, 2 courses of treatment). Of the 23 patients, 20 had received prior chemotherapy. The dominant disease type treated in this trial was colorectal carcinoma (14 cases). Four patients died while on study, in all cases due to progression of cancer. Two of these patients died after a single course of treatment (at 3.5 mg/m^2 and at 6.5 mg/m^2), and two died after a second course of treatment at the highest dose level, 8.1 mg/m^2. The acute toxicity for each of these patients was evaluable since deaths occurred at 28–36 days following the onset of the immediately preceding course of treatment with 2-CdA.

Table 1 Patients' characteristics

Characteristic	Number
Total patients/courses	23/35
MF	11/12
Median age (range)	62 (40–78) years
Performance status (ECOG):	
0	6
1	13
2	4
Prior therapy:	
Chemotherapy	20
Radiation therapy	7
Immunotherapy	2
Disease types:	
Colorectal carcinoma	14
Renal-cell carcinoma	3
Malignant melanoma	2
Soft-tissue sarcoma	2
Small-cell lung cancer	1
Ovarian carcinoma	1

Table 2 Hematological toxicities

	Courses with toxicity: dose level (mg/m^2 per day)			
Toxicity	3.5	5.3	6.5	8.1
Leukopenia (/μl):				
1,000–1999	2	1	4	3
≤ 999	0	0	2	4
Granulocytopenia (/μl):				
500–999	1	0	3	4
≤ 499	0	0	3	3
Lymphocytopenia (/μl):				
500–999	1	3	0	0
≤ 499	9	7	8	7
Thrombocytopenia (/μl):				
25,000–49,999	0	1	0	1
≤ 24,999	2	0	0	3
Anemia (g/dl):				
6.5–7.9	1	0	1	3
< 6.5	0	0	0	1
Total courses	10	10	8	7

Toxicity

The toxicity of therapy with 2-CdA at each dose level is summarized in Table 2. Dose-related hematological toxicity was evident among all blood cell components. Lymphocytes appeared most sensitive to 2-CdA, manifesting profound lymphocytopenia (< 999/μl) at all dose levels tested. It is noteworthy that pretreatment lymphocyte counts for this sample of patients were quite low (median, 1,080/μl; range, 405–1857/μl), perhaps reflecting disease-related immunosuppression or immunosuppression related to prior therapy. None of the treated patients showed evidence of opportunistic infection related to this lymphocytopenia.

The granulocyte series was the next most sensitive cell group to 2-CdA toxicity. Only 1 course among 20 given at the dose levels of 3.5 and 5.3 mg/m^2 per day was accompanied by toxicity exceeding grade 3 granulocytopenia. Of 15 courses of treatment given at 6.5 and 8.1 mg/m^2 per day, 13 induced grade 3 or greater granulocytopenia. The granulocyte nadir usually occurred within 8–16 days of the onset of treatment and resolved promptly by the 28th day of treatment. Two patients treated at 8.1 mg/m^2 per day experienced fever and granulocytopenia requiring hospitalization and antibiotic therapy. Granulocytopenia induced by 2-CdA was the principal toxicity defining the maximum tolerated dose.

Anemia was observed at all dose levels and seemed to become more severe with increasing dose. Similarly, thrombocytopenia occurred with increasing severity as the dose of 2-CdA increased. Among 20 courses of treatment given at dose levels of 3.5 and 5.3 mg/m^2 per day, 3 were accompanied by thrombocytopenia of $< 50{,}000/\mu l$, whereas 4 of 15 courses given at 6.5 and 8.1 mg/m^2 per day produced similar degrees of thrombocytopenia. Platelet nadirs were often delayed (median day of nadir, 24; range, 14–43 days). Platelet recovery was often delayed beyond 28 days; at the dose level of 8.1 mg/m^2 per day, four patients experienced 5–22 days of thrombocytopenia at values below 50,000/μl. One patient treated with a single course of 2-CdA at 6.5 mg/m^2 per day developed thrombocytopenia of 75,000/μl that began 12 days after treatment and persisted for 35 days. Bone marrow biopsy on the 28th day showed normal cellularity and normal representation by all hematopoietic cell lines.

Nonhematological toxicity was sporadic and not clearly related to dose. Nausea, vomiting, anorexia, and fatigue were experienced at all dose levels and were usually well managed with symptomatic medication or observation. Low-grade fever was frequently observed during the 5-day infusion schedule and was unassociated with any infectious etiology. Mild-to-moderate venous phlebitis occurred at the infusion site and often led to venous induration of several weeks' duration. Most patients received 2-CdA infusion by indwelling venous catheter and thus experienced no peripheral vein phlebitis. Episodes of oral mucositis (one patient), diarrhea (one), alopecia (one), hypotension (one), rash (two patients), muscle aches (two), and insomnia (two) accompanied courses of treatment with 2-CdA. Three patients developed hyperbilirubinemia, which exceeded 6 mg/dl in two patients. One patient treated at 3.5 mg/m^2 per day who died on the 27th day of treatment developed severe transaminase and alkaline phosphatase elevation, perhaps as a preterminal event. None of the patients treated in this study manifested evidence of an antitumor effect.

Pharmacokinetic analysis

The pharmacokinetic parameters derived from patients receiving 2-CdA over the dose range of 3.5–8.1 mg/m^2 per day are shown in Table 3. Average plasma concentrations at steady state (Cp_{ss}) ranged from 3.15 ± 0.3 ng/ml at 3.5 mg/m^2 per day to 13.3 ± 2.5 ng/ml at 8.1 mg/m^2 per day. Both Cp_{ss} (Fig. 1) and AUC (Fig. 2) were proportional to dose. A correlation was found between the percentage of change in absolute neutrophil count (ANC) and the AUC for 2-CdA (Fig. 3). It is noteworthy that no patient achieved a peak drug concentration of 2-CdA approaching 1μg/ml, the concentration associated with significant antitumor activity in the human tumor cloning assay [5]. The mean renal excretion of unchanged 2-CdA was $18.2\% \pm 8\%$ over 122 h (Table 4). We found no correlation between the patients' calculated creatinine clearance and the percentage of excretion of 2-CdA ($r = 0.46$, $P < 0.2$).

Table 3 Plasma pharmacokinetics of 2-CdA expressed as mean values ± SD (Cp_{ss} peak plasma concentration at steady state, AUC area under the plasma concentration-time curve, CL plasma clearance)

Patients (n)	Dose (mg/m^2 per day)	Cp_{ss} (ng/ml)	AUC_{24h} (ng h ml^{-1})	CL (l h^{-1} m^{-2})
4	3.5	3.15 ± 0.3	75.5 ± 7.2	46.80 ± 5.1
6	5.3	6.07 ± 1.2	197.2 ± 52	$29.17 + 10.7$
3	6.5	11.22 ± 2.1	269.2 ± 54	25.28 ± 7.0
4	8.1	13.27 ± 2.5	318.4 ± 60	26.31 ± 5.4

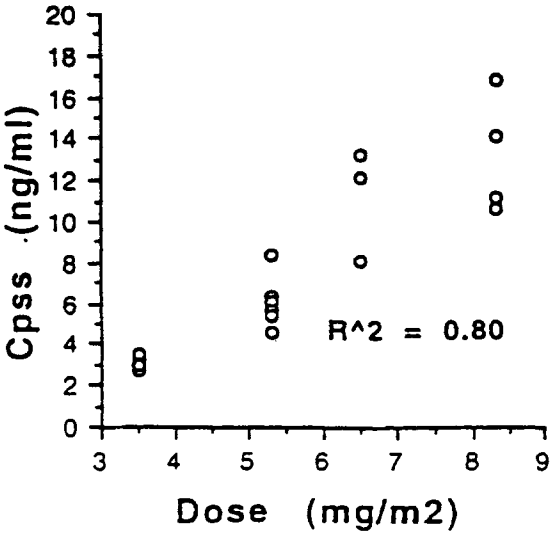

Fig. 1 Peak plasma concentrations of 2-CdA at steady state (Cp_{ss}) versus dose

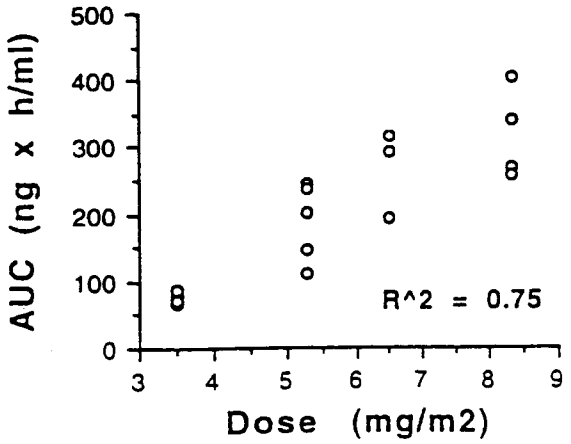

Fig. 2 Area under the plasma concentration-time curve (AUC) of 2-CdA versus dose

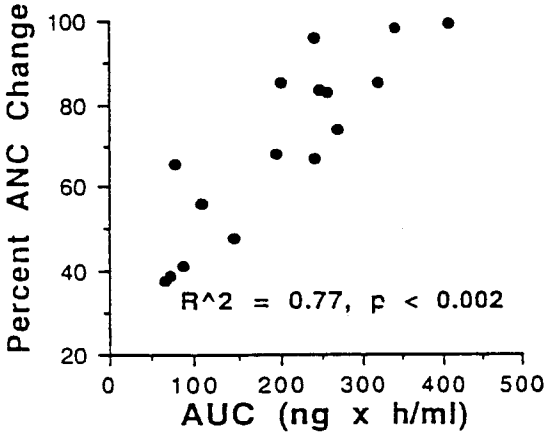

Fig. 3 Percentage of change in absolute neutrophil count (ANC) versus AUC

Table 4 Renal excretion of 2-CdA

Patient	% Excretion 0–24 h	% Cumulative excretion 0–122 h
2	21.0	26.1
4	17.5	23.0
5	11.8	20.3
7	11.0	12.3
8	4.9	13.0
9	16.7	34.7
10	12.7	15.1
11	23.5	22.1
12	9.2	9.5
15	8.2	22.8
16	6.7	11.0
17	8.3	8.2
Mean (± SD)	12.6 (5.9)	18.18 (8.0)

Discussion

The literature is replete with evidence of the substantial therapeutic benefit of 2-CdA against lymphoreticular malignancies, notably hairy-cell leukemia and chronic lymphocytic leukemia. However, there is evidence that 2-CdA may have utility in the treatment of nonlymphoid solid malignancies. Hutton and Von Hoff [5] have shown that substantial in vitro antitumor activity against non-small-cell lung carcinoma, ovarian carcinoma, non-Hodgkins lymphoma, and malignant melanoma accompanies continuous exposure of these tumors to 2-CdA at 1.0 and 10 μg/ml. Saven et al. [16] performed a phase I trial of 2-CdA against nonhematological tumors. A total of 21 patients were exposed to 2-CdA at doses of 0.1–0.2 mg/kg per day by 7-day continuous infusion repeated every 28 days. The maximum tolerated dose was 0.1 mg/kg per day (4 mg/m^2 per day) given for 7 days (28 mg/m^2 cumulative dose), and myelosuppression represented the dose-limiting toxicity. Neurological toxicity occurred in two patients and partial responses were observed in two patients with malignant astrocytomas. Tumor deoxycytidine kinase levels did not correlate with antitumor response. The present study indicated a similar maximum tolerated dose: 6.5 mg/m^2 per day given by continuous infusion over 5 days (32.5 mg/m^2 cumulative dose). No significant evidence of antitumor activity was observed.

Our pharmacokinetic results seem comparable with those obtained in other studies of 2-CdA pharmacokinetics (Table 5). A review of the tabulated pharmacokinetic data on our patients suggested a reliable dose-related increase in Cp_{ss} and AUC. These changes may be correlated with dose-related clinical events (myelosuppression). Although accumulation of the drug was not suggested by these data, prolonged bone marrow suppression was observed at higher doses of 2-CdA, raising concern that the metabolic effects induced by this analogue may be sustained. The observed effects may also reflect the dose-related increase in the 2-CdA AUC, so common with nucleoside antimetabolites.

On the basis of the toxicity data generated in this study, the dose level of 6.5 mg/m^2 per day seems the best tolerated when given by continuous intravenous infusion for 5 days. The emergence of substantial hematological toxicity in patients entered in this clinical trial, the failure to achieve plasma concentrations of 2-CdA associated with antitumor activity in preclinical models, and the absence of observed antitumor activity in this trial do not lead us to recommend this schedule for further investigation. It is unlikely that coadministration of colony-stimulating factors will allow a dose increase consistent with the 2-log increase in plasma concentration associated with predicted antitumor activity.

Table 5 2-CdA pharmacokinetics summary

Study (schedule)	Dose (mg/m^2)	Patients (n)	CP_{ss} (ng/ml)	$t_{1/2\beta}$ (h)	CL ($lh^{-1}m^{-2}$)	AUC (ng $h\,ml^{-1}$)
Liliemark and Juliusson [10] (24 h)	5.2	12	6.4 (± 3.2)	6.7 (± 2.4)	32.8 (derived)	158 (± 74)
Liliemark et al. [11] (2h)	5.2	13	48.3 (± 26)	9.9 (± 4.6)	25.9 (± 7.8)	218 (± 79)
Santana et al. [14] (C.I. × 5 days)	8.9	5	9.9 (5.7–15)	14.2 (3.9–23)	36.1 (23–44)	–
Univ. Texas (C.I. × 5 days)	5.3	6	6.1 (± 1.2)	–	29.2 (± 9.8)	197 (± 52)
Univ. Texas (C.I. × 5 days)	8.1	4	13.3 (± 2.5)	–	26.3 (± 5.4)	318 (± 60)

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