Cancer Chemother Pharmacol (2004) 54: 553–561
DOI 10.1007/s00280-004-0857-3

ORIGINAL ARTICLE

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A phase I trial of gemcitabine plus cladribine in patients with advanced hematologic malignant diseases

Received: 12 November 2003 / Accepted: 29 January 2004 / Published online: 2 September 2004

Abstract *Purpose*: Gemcitabine and cladribine (2CdA) are nucleoside analogues that decrease DNA synthesis via inhibition of ribonucleotide reductase; the combination could be additive or synergistic. We conducted a dose escalation study to establish the maximum tolerable doses (MTD) of gemcitabine and 2CdA when given in combination in patients with advanced hematologic malignancies and to describe the toxicity profile of this combination. *Patients and methods*: A total of 45 patients with advanced hematologic diseases were enrolled into two groups. Group A had adequate baseline hematopoiesis, defined as absolute neutrophil count (ANC) $>1\times10^9$/l and platelet count $>50\times10^9$/l. Group B did not meet these criteria. Hematologic dose-limiting toxicity (DLT) for group A was defined as grade 4 neutropenia or thrombocytopenia lasting >28 days; group B was not evaluated for hematologic toxicity. Nonhematologic DLT was defined similarly for both groups. Death occurring during the first cycle of treatment was considered a DLT event only if it was related to drug toxicity. Gemcitabine was administered as a 4-h intravenous infusion once every 28 days. 2CdA was administered over 1 h daily for the first 3 days of each 28-day cycle. *Results*: The MTD was not reached in either group. Myelosuppression was common, but not dose-limiting. Febrile neutropenia and infections were also common, particularly in group B, and judged in most cases to be due to bone marrow failure at baseline. Nonhematologic toxicities were generally mild, and skin rash, the most frequently observed, was dose-limiting in one patient enrolled in each group. Four deaths (three during the first cycle of treatment) occurred at the highest dose level tested in group B (gemcitabine 5000 mg/m^2 and 2CdA 16 mg/m^2). Although only one of these deaths was dose-limiting by stated criteria, this dose level did not appear to be safely tolerated in this patient population. Several responses were observed in patients with Hodgkin's disease. *Conclusions*: The combination of gemcitabine and 2CdA is feasible in patients with hematologic malignancies. Phase II studies of this combination should be considered, particularly in patients with Hodgkin's disease.

Keywords Cladribine · Gemcitabine · Hematologic malignancy · Combination treatment

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Introduction

Despite the high initial remission rate for many malignant hematologic diseases, the cure rate for most of these diseases is low. Although it is widely believed that there are many good treatments for patients with hematologic malignancies, the low cure rates underscore the need for more rapid identification of active agents and combinations for patients with these diseases.

Gemcitabine (2′,2′-difluorodeoxycytidine) is a pyrimidine nucleoside analog which has been extensively investigated and found to be active in a variety of solid

tumors both as a single agent and in combination with other chemotherapeutics [2, 9, 25]. Recently, gemcitabine, alone or in combination, has been demonstrated to have variable activity in Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL)—particularly, cutaneous T-cell lymphomas—and acute leukemias [7, 21–23, 27, 28]. It is a prodrug that becomes phosphorylated to the active form, 2-difluorodeoxycytidine triphosphate (2dFdCTP) which is incorporated into DNA leading to premature termination of chain elongation. In addition, gemcitabine diphosphate inhibits ribonucleotide reductase (RRase), an enzyme required for DNA replication and repair [20]. Thus, combinations of gemcitabine with other DNA-damaging agents may be effective for hematologic malignancies.

Cladribine (2CdA) is a purine analog with inhibitory effects on DNA synthesis via mechanisms that include inhibition of RRase. 2CdA is effective in hairy cell leukemia and chronic lymphocytic leukemia when given as a continuous infusion at doses of 0.05–0.2 mg/kg per day [18, 19]. Neurotoxicity is dose-limiting when 2CdA is administered in this fashion [26]. The pharmacokinetic profile of 2CdA reveals a biphasic decline in plasma concentrations and a long terminal half-life which supports an intermittent infusion schedule [15]. Our group has demonstrated the tolerability of 2CdA in patients with advanced hematologic malignancies when given as a daily bolus infusion over 1 h for 5 days. The maximum tolerated dose (MTD) was not reached with this schedule despite dose escalation up to 21.5 mg/m^2 per day, though significant myelosuppression was noted at doses ≥15 mg/m^2 per day [14]. A phase II trial of 2CdA conducted at our institution confirmed efficacy (47% response rate) in patients with chronic myeloid leukemia (CML) in accelerated or blast phase disease treated at 15 mg/m^2 per day for 5 days [5].

Gemcitabine induces apoptosis in myeloma cell lines resistant to both steroids and 2CdA [10]. Also, an additive effect of gemcitabine and 2CdA has been demonstrated in murine leukemia cells [17]. No clinical studies investigating this combination have, however, been reported. Based on the hypothesis that combining gemcitabine and 2CdA would be additive or synergistic via maximal inhibition of RRase, we conducted a phase I dose escalation study to investigate the toxicities and feasibility of this combination in patients with advanced hematologic malignancies.

Patients and methods

Patient selection

Patients were eligible for this study if they had histologically confirmed malignant hematologic disease that was refractory to standard therapy or for which no standard therapy existed. Patients had to be 18 years of age or older and have a performance status of 0, 1 or 2 (Cancer and Leukemia Group B, CALGB, criteria). Patients were ineligible if they had a serum creatinine 1.5 mg/dl or greater (or calculated creatinine clearance of less than 60 ml/min) or serum total bilirubin 2.0 mg/dl or greater (unless due to Gilbert's syndrome). Patients were also excluded if they had significant local or systemic infection at the onset of the study, bleeding requiring platelet transfusions, symptomatic CNS disease, pregnancy, or any other significant underlying medical condition that would make administration of either gemcitabine or 2CdA unusually hazardous. In addition, no cytotoxic therapy or radiotherapy was permitted within 2 weeks (6 weeks for mitomycin C and nitrosoureas) of starting therapy with the exception of hydroxyurea, which could be administered up to 72 h prior to the proposed treatment. Patients could not receive warfarin, or steroids (for tumor treatment). The protocol was reviewed and approved by the University of Chicago Institutional Review Board and all patients gave written informed consent.

Study design

This was an open-label, single-center, nonrandomized dose-escalating phase I study. Gemcitabine was administered as a 4-h intravenous infusion on day 1 only, and 2CdA was given as a 1-h bolus infusion for three consecutive days on days 1, 2 and 3 of a 28-day cycle. The first dose of 2CdA was administered immediately prior to the gemcitabine infusion in an effort to harness the hypothesized synergy between the two agents. Patients were divided into two groups upon study entry. Group A included patients with adequate hematopoiesis at study entry as defined by an absolute neutrophil count (ANC) $> 1\times10^9$/l and a platelet count $> 50\times10^9$/l. Group B included all other patients who did not meet the criteria for ANC and platelet count required for group A (Table 1).

A gemcitabine starting dose of 3600 mg/m^2 was chosen based on prior data from the every 2-week schedule that also employed a 4-h infusion [1, 13]. The MTD in that study was 3600 mg/m^2 given once every 2 weeks and the dose-limiting toxicity (DLT) was reversible hematologic toxicities in patients with solid tumors.

Our initial design called for an escalation of the gemcitabine dose by increments of 20–25% (while keeping the 2CdA dose fixed) until the MTD was established (Table 2). Enrollment of subsequent patients at one dose level below the MTD (of gemcitabine) would then occur while escalating the dose of 2CdA, also by increments of 20–25%. The 2CdA starting dose of 8 mg/m^2 per day for 3 days (24 mg/m^2 over each 3-day course) was approximately 25% of the MTD in our previous phase I trial of 2CdA as a single agent in patients with hematologic malignancies (107.5 mg/m^2 over a 5-day course) [14]. 2CdA dose escalation was to proceed until the MTD was reached. Intrapatient dose escalation to the next higher dose level was permitted (criteria listed in Table 3) in patients who had not

Table 1 Patient characteristics

	Group A	Group B
No. of patients enrolled	20	25
No. of evaluable patients	20	25
No. of cycles administered		
Total	43	34
Median (range)	1 (1–6)	1 (1–4)
Age (years)		
Median	58	62
Range	21–71	27–78
Sex (M/F)	10/10	13/12
Prior therapy		
Chemotherapy	20	24
Radiation therapy	12	4
Autologous stem cell transplantation	6	5
Allogeneic stem cell transplantation	3	1
Diagnoses		
Hodgkin's disease (HD)	5	1
Non-Hodgkin's lymphoma (NHL)	8	1
Acute lymphoblastic leukemia	2	4
Acute myeloid leukemia or myelodysplasia	3	18
Chronic myeloid leukemia (CML)	1	0
Multiple myeloma	1	1
Stage of disease		
Previously untreated	0	1
Relapsed	11	18
Primary refractory	8	6

experienced a DLT and whose disease was stable or who had responded to therapy.

During the course of the study, the study was amended to stop the escalation of gemcitabine and to administer the dose level being investigated at that time even though the MTD of gemcitabine had not been reached (this was dose level 2A and 2B in each group, respectively; Table 2). This decision was made because of data indicating that the formation of gemcitabine triphosphate is saturable at dose rates exceeding 700 mg/m^2 per hour [11, 12]; therefore, an increase in the unit dose beyond 4200–5000 mg/m^2 per 4 h would be unlikely to lead to an increase in drug exposure. The 2CdA dose was then escalated while keeping the gemcitabine dose fixed at the levels (4200 mg/m^2 for group A and 5000 mg/m^2 for group B) shown in Table 2.

Decisions regarding additional treatment after the first cycle were made according to evidence of response and the presence or absence of dose-limiting toxicities as described in Table 3. Patients who had stable or responding disease after four cycles of therapy could receive additional cycles at the investigator's discretion.

Dose escalation and definition of study endpoints

DLT for group A or B patients was any grade 3 or greater nonhematologic toxicity (except transient liver function abnormalities), or any grade 2 or greater neurologic or pulmonary toxicity (which are specific toxicities for single-agent 2CdA or gemcitabine, respectively) probably or definitely related to gemcitabine or 2CdA. Dose-limiting hematologic toxicity in group A patients was defined as grade 4 neutropenia or thrombocytopenia persisting beyond 28 days unless due to progressive disease in the marrow. The severity of hematologic toxicity was not used to define DLT in group B patients, because these patients already had bone marrow failure at entry to the study, either as a result of advanced disease or extensive prior therapy. Any death due to toxicity arising from treatment on the study was also considered a DLT event.

A minimum of one patient was evaluated at each dose level if no DLT and no nonhematologic toxicity of more than grade 2 were observed. One patient from group A had to be fully evaluable (observed for at least 4 weeks) at each dose level before further group A patients could receive a higher dose. After one episode of DLT was observed, a minimum of three patients were enrolled at subsequent dose levels. Patients from group B followed the same dose-escalation patterns as those from group A; however, if group A patients had safely tolerated a particular dose level without experiencing nonhematologic DLT, then a group B patient could start at the next higher dose level. If one of the first three patients at a dose level experienced DLT, then at least three additional patients were treated at that dose level to determine if the MTD had been exceeded. Fewer than three additional patients would be enrolled if the MTD were

Table 2 Dose levels

	Dose level	Gemcitabine (mg/m^2×1 day)	2CdA (mg/m^2×3 days)	No. of patients	No. of courses
Group A	1A	3600	8	1	1
	2A	4200	8	4[a]	14
	3A	4200	10	9[b]	17
	4A	4200	12.5	6	11
Group B	1B	4200	8	4	5
	2B	5000	8	4	7
	3B	5000	10	2	3
	4B	5000	12.5	8	11
	5B	5000	16	7	8

[a]Intrapatient dose escalation occurred in one patient with HD who had a PR after two cycles of treatment. Gemcitabine dose was increased to 5000 mg/m^2 per day for the subsequent two cycles

[b]Intrapatient dose escalation of 2CdA dose to 12.5 mg/m^2 in one patient with refractory AML with stable disease but no DLT after two cycles of treatment

Table 3 Treatment decision based upon disease response and DLT status

Disease status	DLT observed	Action for the patient
Clinical response after first course	No	Continue at same dose
Stable disease after first course	No	Continue at same dose
Clinical response or stable disease after two or more courses	No	Increase one dose level if next dose does not exceed the MTD
Clinical response or stable disease after first course	Yes	Decrease one dose level and repeat treatment
Clinical response after two or more courses	Yes	Decrease one dose level and repeat treatment
Stable disease after two or more courses	Yes	Withdraw patient from study
Progressive disease after first course	No	Continue at same dose
Progressive disease after two or more courses	–	Withdraw patient from study

clearly exceeded before six patients had been treated. If none of the first three patients at a dose level experienced DLT, then dose escalation could proceed to the next level. The MTD was defined as the dose at which at least two (33%) of six patients experienced first course DLT. The recommended phase II dose was defined as one dose level below the MTD. Toxicity was graded according to the CALGB expanded common toxicity criteria.

Pretreatment and follow-up studies

Within 4 weeks of starting therapy, each patient underwent a detailed evaluation which included the following: history and physical examination, chest radiograph, CT scans of areas of known disease (for patients with lymphoma), prothrombin time, partial thromboplastin time, fibrinogen, serum amylase, and electrocardiogram. A pretreatment bone marrow aspiration and biopsy was performed on all patients within 4 weeks of starting therapy. Complete blood cell count (CBC) with differential and platelets and serum chemistries including liver and renal function tests were obtained within 2 weeks prior to the start of treatment.

In general, patients received treatment in the outpatient area, but could be hospitalized if the treating physician considered this to be necessary. CBC and serum chemistries were performed on the first day of each cycle and monitored at least twice weekly during the treatment week and weekly thereafter. Symptom assessment and physical examination were performed at least once a week. A follow-up bone marrow examination was performed between days 13 and 15 of the first course of treatment in patients with acute leukemia. Response was assessed after every one to two cycles of therapy. Re-evaluation CT scans and chest radiographs were performed, if clinically indicated, after every two cycles to assess response.

For the purposes of this study, complete response (CR) was defined as the absence of any discernible disease by physical examination, laboratory, or radiographic evaluation. In addition, a CR had to have an ANC $\geq 1\times10^9$/l and a platelet count $\geq 100\times10^9$/l. The bone marrow examination had to reveal less than 5% blasts with trilineage hematopoiesis and an overall cellularity of $>20\%$. The response had to be maintained for more than 4 weeks. A partial response (PR) was defined as a 50% or greater reduction of known disease in extramedullary sites. Bone marrow examination had to reveal a 50% decrease in abnormal cells from the initial examination if the marrow had been involved with disease, and there had to be some evidence of normal hematopoietic activity. Responses had to last more than 4 weeks. A minor xresponse (MR) was any response less than a PR but more than no response. No response (NR) was defined as no evidence of response to drug. Progressive disease (PD) was defined as a 25% or greater increase of known disease in extramedullary sites. Bone marrow examination had to reveal a 25% increase in abnormal cells from the initial examination if the marrow was involved with disease. For solid lesions (for example, lymphoma) an increase of 25% or more in the sum of the products of the longest perpendicular diameters of all measured indicator lesions compared to the smallest previous measurement or the appearance of a new lesion were required.

Statistical methods

Potential predictors for non-hematologic toxicities were examined. This analysis was largely exploratory in nature. Variables assessed for prediction of toxicity included the following: age, study group (A/B), pretreatment platelet count ($\times10^9$/l) and neutrophil count ($\times10^9$/l), 2CdA dose (mg/m^2 per day) and gemcitabine dose (mg/m^2 per day). Because of the small sample size, Fisher's exact test was used for categorical variables and Wilcoxon's rank-sum test was used for continuous variables [4].

Results

Patient characteristics

A total of 45 patients were enrolled, 20 in group A and 25 in group B. Patient characteristics are summarized in Table 1. Eight patients in group A received more than

Table 4 Grade 3/4 toxicities in group A

Gemcitabine/2CdA (mg/m^2/day)	No. of patients	Neutropenia grade 4	Thrombocytopenia grade 4	Infection grade 3/4	Neutropenic fever grade 3/4	Rash grade 3/4
3600/8	1	–	1	–	–	–
4200/8	4	4	1	1	1[a]	–
4200/10	9	8	5	–	2[b]	1[c]
4200/12.5	6	6	3	4[c]	–	–

[a]Onset of grade 2 fever was within 24 h of initiating therapy and persisted through the period of neutropenia.
[b]Culture-negative febrile neutropenia occurring after two or more cycles of therapy.
[c]Includes one DLT

one cycle of therapy; two of these patients received six cycles of therapy which was the maximum administered on the study; one patient received five cycles, and one patient received four cycles of therapy. Seven patients in group B received more than one cycle of therapy; one received four cycles of therapy, and six patients received two cycles of therapy. Intrapatient dose escalation occurred in two patients, both of whom were in group A (Table 2). The most common reason for receiving only one cycle of therapy in both treatment groups was disease progression.

Hematologic toxicity

Patients in group A had adequate hematopoiesis (ANC $>1\times10^9$/l and platelet count $>50\times10^9$/l) and were, therefore, considered evaluable for hematologic toxicity. The median ANC at baseline for patients in this group was 5.2×10^9/l (range 1.2–9.5×10^9/l), and the median platelet count was 183×10^9/l (range 58–810×10^9/l).

As expected, the combination was quite myelosuppressive with all 20 patients in the group experiencing grade 3 or 4 neutropenia (Tables 4 and 5): 2 patients had grade 3 neutropenia (1 patient at the first dose level and 1 patient at the third dose level), and 18 patients had grade 4 neutropenia. The median time to ANC and platelet recovery to baseline levels after the first cycle of therapy was 22 days for both parameters (ranges 13–41 days and 15–26 days, respectively). Hematologic DLT was, however, not reached in any patient because grade 4 hematologic toxicity resolved in all evaluable patients in the group prior to day 28 of the first cycle of therapy. The median time to recovery of both ANC ($>1\times10^9$/l) and platelets ($>50\times10^9$/l) was 18 days (range 11–28 days). Three patients, whose disease had relapsed after prior allogeneic bone marrow transplantation, were not fully evaluable for toxicity because they were taken off the study to receive donor lymphocyte infusions on days 16, 19, and 20, respectively, of cycle 1. Of the 17 evaluable patients, 16 showed blood count recovery by the end of cycle 1 (day 28) to levels that would permit administration of a subsequent cycle of therapy. One patient with NHL developed gram-negative sepsis during the first cycle of therapy and failed to show recovery of her platelet count to baseline levels until day 41.

Group B patients were not evaluated for hematologic DLT due to bone marrow failure at baseline. The median ANC at baseline in these patients was 1.1×10^9/l (range 0–17.4×10^9/l), and the median platelet count was 23×10^9/l (range 3–115×10^9/l).

Nonhematologic toxicity

Common grade 1/2 toxicities seen in both groups included fatigue ($n=8$) and rash ($n=8$). Less common toxicities included transient liver function abnormalities ($n=2$), alopecia ($n=2$) and mucositis ($n=2$). There was one episode each of grade 1 neurotoxicity (transient dysesthesias occurring in a patient in group A after two cycles of therapy at dose level 2A) and grade 2 hypercalcemia.

Apart from infections (described in detail below), severe adverse events were infrequent. Grade 3/4 nonhematologic toxicity included rashes (one patient in each group) which were dose-limiting (Tables 4 and 6). Each of these patients received a second cycle of treatment at a reduced dose (one dose level lower) without recurrence of toxicity. There were two episodes of grade 3 or greater cardiac adverse events, both of which occurred in group B (Table 6) and included atrial fibrillation occurring in the context of *Pseudomonas* bacteremia following the second cycle of therapy in a patient with refractory AML. The arrhythmia was judged secondary to ongoing bacteremia rather than treatment-related cardiotoxicity. The other episode was a case of fatal ventricular fibrillation occurring on day 1 of therapy and presumed

Table 5 Hematologic toxicity following the first course in group A

Gemcitabine/2CdA (mg/m^2/day)	No. of patients	ANC nadir ($\times10^9$/l)		Platelet nadir ($\times10^3$/μl)	
		Median	Range	Median	Range
3600/8	1	0.8	–	20	–
4200/8	4	0.19	0.02–0.3	46	16–84
4200/10	9	0.06	0.0–0.7	21	8–82
4200/12.5	6	0.19	0.1–0.7	28.5	8–138

Table 6 Grade 3/4 toxicities in group B

Gemcitabine/2CdA (mg/m^2/day)	No. of patients	Infection	Febrile neutropenia	Pulmonary (grade ≥2)	Rash	Fatigue	Liver function	Cardiac
4200/8	4[a]	1	2	–	–	1	–	–
5000/8	4	–	1	–	–	–	–	–
5000/10	2	1	–	–	–	–	–	1
5000/12.5	8	–	4	–	1[b]	–	1	–
5000/16	7	2[b]	1	2	–	–	–	1

[a]Includes one patient with intracranial hemorrhage in the setting of severe baseline thrombocytopenia during the first cycle of therapy
[b]Includes one DLT

to be secondary to sepsis in a patient with relapsed AML, baseline ANC of 0, and a preexisting neutropenic fever.

There were two episodes of grade 2 or greater pulmonary adverse events (Table 6); both occurred in group B and were related to the patient's underlying disease. These included worsening of baseline hypoxemia in a patient with pulmonary involvement by HD and extensive prior therapy including radiation therapy to the mediastinum. The second patient had respiratory failure secondary to a malignant pleural effusion complicated by a pneumothorax. Grade 3 liver function abnormalities were observed in one patient, but these were transient and not dose-limiting. Severe mucositis was not observed.

There were no episodes of severe treatment-related neurotoxicity. However, one patient in group B developed intracranial hemorrhage (Table 6); the pretreatment platelet count was 14×10^9/l, and the platelet count was 10×10^9/l at the time of the event.

Infections and febrile neutropenia

There were several episodes of grade 3/4 infection (Table 7) that were judged to have occurred as a result of the patient's underlying disease state or other factors unrelated to the treatment. Only two of these infections were dose-limiting. They included a patient with relapsed NHL who developed gram-negative sepsis (*Achromobacter* species) while neutropenic following treatment at the highest dose level explored in group A. This patient had a baseline ANC of 6×10^9/l. The other episode of infection that was dose-limiting occurred in a patient in group B who developed clostridium sepsis associated with a leukemoid reaction (ANC peaked at 70×10^9/l) on day 15 of cycle 1. This patient had AML in second relapse, with a baseline ANC of 7.75×10^9/l and platelet count of 5×10^9/l.

There were 11 episodes of culture-negative febrile neutropenia; nine of these occurred in patients with AML, eight of whom were in group B. The median pretreatment ANC in the 11 patients with neutropenic fever was 0.5×10^9/l compared with 4×10^9/l for the 34 patients without neutropenic fever. In most cases these episodes of febrile neutropenia were judged to be secondary to the patients' underlying disease state and compromised hematopoiesis. As expected, a low baseline ANC correlated with the development of febrile neutropenia ($P=0.0016$, Wilcoxon's rank-sum test). However, there was no relationship between dose and the development of infections or febrile neutropenia.

Table 7 Infections following treatment

	Gemcitabine/2CdA (mg/m^2/day)	No. of patients	No. of courses	No. of infections	Infection (site: organism)
Group A	3600/8	1	1	0	
	4200/8	4	14	1	Thrombophlebitis and endocarditis: *Staphylococcus aureus*
	4200/10	9	17	0	
	4200/12.5	6	11	5	Central venous catheter tunnel infection, submandibular abscess[a]. Skin[a]: herpes zoster. Blood[b]: *Achromobacter* (*Alcaligenes*) *xylosoxidans*. Cellulitis[a]
Group B	4200/8	4	4	1	Pneumonia[a]: *Aspergillus*
	5000/8	4	7	0	
	5000/10	2	3	1	Blood: *Pseudomonas*
	5000/12.5	8	11	1	Oral: *Candida*
	5000/16	7	8	3	Blood[b]: *Clostridium tertium*[c]. Blood[a]: methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*[c]. Colon: *Clostridium difficile*

[a]Infections occurring following two or more cycles of therapy
[b]Dose-limiting
[c]Fatal

Older age was significantly associated with the incidence of infection ($P = 0.019$, Wilcoxon's rank-sum test).

There were four deaths on study, all occurring at the highest dose level explored in group B (5000 mg/m^2 of gemcitabine and 16 mg/m^2 per day for three doses of 2CdA). Only one of these was dose-limiting and occurred in the patient with relapsed AML who developed clostridium sepsis (described above). The other death directly related to a proven infection occurred in a patient who tolerated the first cycle of therapy, but died from sepsis (methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*) following the second cycle of therapy (Table 7). There was evidence of cumulative myelosuppression in this patient; baseline ANC was over 1×10^9/l, but this had dropped to 0.3×10^9/l by day 1 of cycle 2.

The other two deaths on study were judged to be either secondary to presumed sepsis arising as a result of impaired baseline hematopoiesis (hypotension, ventricular fibrillation, and death occurring on day 1 of therapy in a patient with relapsed AML and a baseline ANC of 0) or directly related to the patient's disease (respiratory failure secondary to a malignant pleural effusion and pneumothorax in a patient with NHL). Both of these cases were also described above as cardiac or pulmonary adverse events which were unrelated to drug therapy.

Clinical responses

Response was a secondary endpoint of this study. The best objective responses observed are listed in Table 8. Four of six patients with HD had a response (two CRs and two PRs). These patients all had relapsed or refractory disease, all had received three or more chemotherapeutic regimens plus involved field radiation therapy. Three of these four responders with HD had also previously had an autologous stem cell transplant. One patient with primary refractory AML and a prior history of myelodysplastic syndrome had a partial response with greater than 50% decrease in bone marrow blasts following three cycles of therapy, and achieved normalization of his peripheral blood counts after a fourth cycle of therapy at the same dose level. Minor responses were noted in two other patients. One of these patients had AML and had relapsed after an allogeneic stem cell transplant; this patient had significant cytoreduction to less than 5% marrow blasts and went on to receive an infusion of donor lymphocytes.

Discussion

This phase I dose escalation study demonstrated that the combination of gemcitabine and 2CdA is feasible in patients with advanced hematologic malignancies with and without adequate hematopoiesis. Myelosuppression was common and was uniformly demonstrable in patients with adequate hematopoiesis. Infections and febrile neutropenia were also common, with a higher incidence in older patients and those with bone marrow failure at baseline, respectively, and did not correlate with drug dosage. Thus, it is not possible to recommend specific dosages on the basis of toxicity observed in this trial. Although we did not identify the MTD applying the strict criteria of our study design, there were several adverse events including four deaths observed at the highest dose level tested in group B. A clear causative link between the treatment and these events could not be established because of confounding baseline host factors in this population of patients; however, as this dose level (5000 mg/m^2 per day of gemcitabine and 16 mg/m^2 per day of 2CdA for 3 days) was not safely tolerated, it cannot be recommended for broader testing without further evaluation of its safety. The trend toward an increased number of infections (five episodes in six patients) at the highest dose level explored in group A (4200 mg/m^2 per day of gemcitabine and 12.5 mg/m^2 per day of 2CdA) led to a decision to halt further dose escalation in this group. The majority of these infections occurred following two or more cycles of therapy.

The study illustrates the advantages of incorporating a design that stratified patients into two groups depending on the presence or absence of adequate hematopoiesis at baseline. This strategy was employed because many patients with hematologic malignancies, unlike patients with solid tumors enrolled in phase I trials who are typically required to have normal hematopoietic function at baseline, often have severe cytopenias upon trial enrollment due to their underlying disease and/or prior therapy, and, therefore, hematologic toxicities cannot always be assessed. However, some candidates for such trials do in fact have adequate blood counts at study entry. Therefore, the concept of stratification according to blood counts at study entry

Table 8 Response in seven patients by group and dose level

Response	Group	Gemcitabine/2CdA (mg/m^2/day)	No. of courses	Diagnosis
CR	A	4200/8	6	HD–refractory
	A	4200/8	6	HD–relapsed
PR	A	4200/10	5	HD–refractory
	A	4200/10	2	HD–relapsed
	B	5000/8	4	AML–refractory
Minor	A	4200/10	1	AML–relapsed
	B	4200/8	2	Multiple myeloma–relapsed

was a rational first step toward defining the degree of treatment-induced myelosuppression in such patients, and allowed us to demonstrate clearly the universal myelosuppression induced by this combination even in patients with adequate hematopoiesis at baseline. We observed grade 3/4 myelosuppression from gemcitabine and 2CdA in all of these patients, but each episode was transient, and none of the episodes occurring during the first cycle were dose-limiting.

The accelerated titration design employed in this study allowed fewer patients to be treated at the lower dose levels [24]. Intrapatient dose escalation [16] allowed patients with stable or responding disease after two cycles the opportunity to be treated at the next higher dose level provided this had not exceeded the MTD. Using this strategy, a patient with HD who achieved a PR after two cycles was treated for four additional cycles at the next higher dose level and subsequently achieved a CR, thus illustrating the potential advantage of incorporating this feature (intrapatient dose escalation) into the design of early phase clinical trials. However, intrapatient dose escalations obscure detection of dose-dependent late or cumulative toxicity, which was not an issue in this study.

The responses seen in HD were quite encouraging. However, it is unclear whether these responses were due to gemcitabine alone, or the combination. Gemcitabine is an active agent in HD; the earliest single-agent phase II trials showed a 39% response rate, and 9% were complete responses [23]. Patients who had received a prior autologous stem cell transplant were excluded from that study. A smaller phase II study involving 14 patients with relapsed or refractory HD showed an overall response rate of 43%; two patients had a CR [29]. Other trials combining gemcitabine with platinum compounds in patients with multiply relapsed HD and NHL have shown good results with overall response rates in the 50–80% range [3, 6]. Larger phase II trials combining gemcitabine with anthracycline-based regimens in relapsed HD are ongoing; results from these are pending.

Proposals for moving gemcitabine into frontline combination therapy for newly diagnosed HD have also been developed. Twelve patients were enrolled on one of such trials in which gemcitabine was substituted for dacarbazine in the standard (Adriamycin, bleomycin, vinblastine, dacarbazine) regimen in patients with newly diagnosed high-risk HD [8]. Of 12 patients in that trial, 5 (40%) developed clinically significant pulmonary toxicity and the authors concluded that the bleomycin/gemcitabine combination should not be pursued for de novo HD due to significant pulmonary toxicity [8]. Though the numbers in this study were too small to determine whether the combination of gemcitabine and 2CdA demonstrates synergy in HD, we believe the responses and acceptable toxicity profile seen in our very heavily pretreated group of patients make the regimen worthy of further study in patients with relapsed or refractory HD. The exclusion of an anthracycline from this regimen may make it an attractive feature especially for patients who have had significant prior exposure to anthracyclines or marginal cardiac function.

Acknowledgements This work was supported in part by research contracts with Ortho Biotech, Inc., (LE96-59-012) and Eli Lilly and Company (B9E-MC-I020), and by grant number CA-14599 from the National Cancer Institute, Bethesda, MD, USA.

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