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Clinical report

Gemcitabine and interferon-α2b in solid tumors: a phase I study in patients with advanced or metastatic non-small cell lung, ovarian, pancreatic or renal cancer

Stefan Fuxius,[1] Klaus Mross,[1] Kambiz Mansouri[2] and Clemens Unger[1]
[1]Tumor Biology Center, Albert-Ludwigs-University Freiburg, 79106 Freiburg i Br, Germany.
[2]Lilly Deutschland, 61350 Bad Homburg, Germany.

We performed a phase I study combining gemcitabine and interferon (IFN)-α2b in patients with advanced solid tumors to determine the maximum tolerated dose (MTD) and recommended doses for phase II trials. Five dose levels of gemcitabine (mg/m^2)/IFN-α ($\times 10^6$ IU) were planned: 500/5, 1000/5, 1000/7, 1000/10 and 1200/10. Gemcitabine was given once weekly and IFNα 3 $\times$ weekly for 3 consecutive weeks followed by 1 week of rest (28-day cycles). Between February 1997 and June 1999, 21 patients with advanced pancreatic (n=3), ovarian (n=1), renal (n=10) and non-small cell lung cancer (NSCLC; n=7) were enrolled. The MTD was reached at gemcitabine 1000 mg/m^2 and IFN-α 7 $\times$ 10^6 IU, with two of three patients having dose-limiting toxicity (thrombocytopenia). The predominant hematologic toxicities (grade 3/4) were neutropenia and thrombocytopenia (13 and five patients, respectively). Three patients had moderate neutropenic fever and one had grade 4 AST/ALT; none required hospitalization. Of the 18 evaluable patients, responses included one partial response (NSCLC) and 10 stable diseases (eight renal cancer). We conclude that the recommended phase II study regimen is gemcitabine 1000 mg/m^2 and IFN-α 5 $\times 10^6$ IU, every 28 days. The results, particularly those in metastatic renal carcinoma, are encouraging and worthy of further evaluation in phase II trials. [© 2002 Lippincott Williams & Wilkins.]

Key words: Gemcitabine, immunotherapy, interferon, phase I, solid tumors.

Introduction

Gemcitabine, a pyrimidine antimetabolite,[1] is active across a range of human solid tumors,[2] including non-small cell lung cancer (NSCLC),[3] pancreatic cancer,[4,5] bladder cancer,[6] advanced breast carcinoma,[7] cisplatin-refractory ovarian carcinoma,[8] and head and neck cancer.[9] In clinical trials, 800–1250 mg/m^2 gemcitabine given on days 1, 8 and 15 of a 28-day schedule[10,11] was well tolerated with short-lived myelosuppression, and reversible and mild elevations in hepatic transaminases and proteinuria, mild skin rash with and without pruritus, and manageable nausea and vomiting. Pulmonary toxicity rarely occurs.[12]

Interferons (IFNs) are cytokines that are naturally occurring small proteins and glycoproteins produced and secreted by virtually all eukaryotic cells. Once produced, IFNs induce antiviral, antimicrobial, antitumor and immunomodulatory effects.[13–17] IFNs induce their cellular activities by binding to specific membrane receptors on cell surfaces. Receptor binding activates cytoplasmic signals that induce the nucleus to stimulate genes encoding a number of proteins with defense actions.

Three major classes of IFNs (α, β and γ) have been identified, based primarily on their antigenic properties. These classes are not homogeneous and may contain several different molecular species. IFN-γ (type II) is principally an immunomodulatory agent. IFN-α and -β (type I) appear to share the same membrane receptor, which is distinct from the gamma receptor, and thus exert similar effects.

IFN-α and -β have mainly been studied in the treatment of various tumors and hepatitis. IFN-γs are used in the treatment of chronic granulomatous disease and IFN-βs are used primarily in the treatment for multiple sclerosis. IFN-αs, such as α2b, have been applied widely for the treatment of various malignancies, particularly blood malignancies

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Correspondence to S Fuxius, Tumor Biology Center, Albert-Ludwigs-University Freiburg, Breisacherstrasse 117, 79106 Freiburg i Br, Germany.
Tel: (+49) 761386870; Fax: (+49) 7613868710;
E-mail: stefanfuxius@gmx.de

including hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic myelogenous leukemia, low-grade and intermediate-grade non-Hodgkin lymphoma, melanoma, and myeloma.[18,19] IFN-α2b has been registered in several countries for the treatment of patients with carcinoid tumors because of its ability to stimulate the natural killer mechanisms in the cell to control secretion of tumor products and tumor cell proliferation, and thus ameliorate clinical symptoms.

The most common adverse events associated with IFNs include flu-like symptoms (including fever, malaise, myalgia and headache), hepatic dysfunction, renal dysfunction, gastrointestinal events (including nausea/vomiting and diarrhea), central nervous system symptoms, leukopenia/granulocytopenia and cardiovascular events (including cardiac insufficiency and arrhythmia).[20]

Preclinical data have shown synergistic effects of gemcitabine and IFN-α2b.[21,22] On the basis of the activity-enhancing potential of either agent when combined, we evaluated regimens of gemcitabine plus IFN-α2b in this initial phase I study in a variety of solid tumors (NSCLC, ovarian, pancreatic and renal cancer).

The primary objectives of this phase I study were to determine the dose-limiting toxicity (DLT), the maximum tolerated dose (MTD), and the recommended doses of gemcitabine and IFN-α2b for subsequent clinical phase II studies. Secondary objectives include the characterization of the overall toxicity profile and the combination's antitumor activity.

Materials and methods

Inclusion criteria

All patients had to have a histologic or cytologic diagnosis of locally advanced or metastatic NSCLC, ovarian, pancreatic or renal cancer. Patients from 18 to 80 years of age with a predicted life expectancy of at least 3 months and a Karnofsky performance status of at least 60 were included. Patients were allowed to have had up to two previous chemotherapy regimens, provided they discontinued previous therapy at least 3 weeks prior to study start and recovered from the toxic effects of the treatment. No other form of therapy, such as radiotherapy, was allowed for at least 3 weeks before enrollment in the study. Adequate bone marrow reserve [white blood cell (WBC) count 3.5×10^9/l, platelets 90×10^9/l, hemoglobin 100 g/l], liver function [bilirubin 1.5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) 3 times the ULN or 5 times the ULN in patients with metastatic liver disease] and renal function (serum creatinine within 1.5 times the ULN) were required. Patient compliance and geographic proximity had to allow for adequate follow-up. In females, the child-bearing potential had to be either terminated by surgery, radiotherapy or menopause, or attenuated by use of an approved contraceptive method during and for 3 months after the trial.

Patients were excluded from the trial if they were receiving concomitant cytotoxic therapy, hormonal treatment, immunotherapy or an experimental agent. Further exclusion criteria included active central nervous system metastases, active infection, serious concomitant systemic disorders, congestive heart failure [New York Heart Association (NYHA) class III and IV], uncontrolled hypertension, unstable angina, severe arrhythmias and intolerance to human protein.

The study was conducted according to the Declaration of Helsinki and existing rules for Good Clinical Practice.[23] The local ethics committee approved the study and written informed consent was obtained from all patients.

Treatment and dose escalation

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) dose was calculated from the body surface area of the patient, and was given as a 30-min i.v. infusion once weekly (days 1, 8 and 15). IFN-α2b (Intron; Essex Pharma, Munich, Germany) was given s.c. as an absolute dose 3 × weekly (days 1, 3, 5, 8, 10, 12, 15, 17 and 19). The 3-week dosing interval was followed by 1 week of rest to form a 28-day cycle.

Between 2 and 14 total cycles were given or until disease progression or unacceptable toxicity was noted. Patient compliance to IFN-α2b was measured with diary cards. Patients received full supportive care, including paracetamol (500–1000 mg 30 min before IFN-α2b infusion, not to exceed 4000 mg/day) as prophylaxis for flu-like symptoms.

Three to six patients were to be treated at each dose level. Five dose levels of gemcitabine (mg/m^2)/IFN-α2b ($\times 10^6$ IU) were planned: level 1, 500/5; level 2, 1000/5; level 3, 1000/7; level 4, 1000/10 and level 5, 1200/10. Doses were not escalated within a single patient during subsequent cycles. The MTD was reached if any of the following events happened

to two or more of the six patients during the first cycle of therapy: WHO grade 4 leukopenia, grade 4 thrombocytopenia and grade 3/4 non-hematologic toxicity (except grade 3/4 alopecia, grade 3 nausea/vomiting, grade 3 musculoskeletal pain or grade 3 mucositis). If patients displayed toxicity that did not meet the above criteria but fulfilled the criteria for dose adjustment, the determination of whether this toxicity was representative of the MTD was at the discretion of the investigator. For example, if two or more patients per dose level required dose adjustments in the first cycle of therapy, the investigator could determine the toxicity to be dose limiting.

At dose levels in which none of the patients experienced any MTD-defining toxicities, a maximum of three patients were treated. If hematologic toxicity WHO grade 3 or non-hematologic toxicity (excluding alopecia and nausea/vomiting) WHO grade $\geqslant 2$ occurred in one patient at a given dose level, additional patients were added to this dose level up to a maximum of six patients. If no DLT was observed, dose escalation was continued. If DLT occurred in at least two patients, dose escalation was stopped, establishing the MTD at this level, and five additional patients were treated at the previous dose level. If, at this dose level, DLT occurred in two of eight or three of 11 patients, this dose level represented the recommended dose for subsequent phase II studies. Doses were not escalated within a single patient during subsequent cycles.

Dose adjustments within cycles and for subsequent cycles were based on weekly WBC counts, platelet counts and non-hematologic grade 3/4 toxicities. For a WBC count of 0.5 to 1.49×10^9/l or a platelet count of 50 to 74×10^9/l, both medications were reduced by 50%; for a WBC count $< 0.5 \times 10^9$/l or a platelet count $< 50 \times 10^9$/l, doses were withheld. For subsequent cycles, patients who sustained febrile neutropenia, grade 4 thrombocytopenia or bleeding associated with thrombocytopenia were to receive 50% of the starting doses of the previous cycle. For grade 3/4 non-hematologic toxicities, doses were either reduced by 50% or withheld. Missed doses were not given at a later time. A patient who could not be administered treatment for 6 weeks from the time of the last treatment was to be discontinued from the study.

Baseline and follow-up assessments

Disease status was assessed before and during the study with the following procedures: medical history and physical examination, evaluation of Karnofsky performance status, tumor measurement of palpable or visible lesions, chest X-ray, radiologic tests (computed tomography scan, magnetic resonance imaging, nuclear medicine scan or ultrasound), hematology and differential blood cell counts, blood chemistries, urinalysis, electrocardiogram, and vital signs. The same assessment method used to determine baseline disease status was used consistently throughout the study.

Toxicity and response assessments were based on standard WHO criteria. All eligible patients who received at least one dose of gemcitabine or IFN-α2b were evaluated for toxicity at the end of each cycle. All eligible patients treated with at least 1 cycle of gemcitabine and IFN-α2b were evaluated for response. Response was assessed before every other therapy cycle.

Results

Patient characteristics

From February 1997 to June 1999, a total of 21 Caucasian patients (three with pancreatic, one with ovarian, 10 with renal and seven with NSCL cancer), nine females and 12 males, entered the trial. Three patients were discontinued from the study before completing 1 cycle of therapy because of DLT in two patients (with pancreatic and ovarian cancer, respectively) and uncontrolled infection (with NSCLC) in the other, and thus were not included in the response evaluation. The latter patient was also excluded from the MTD evaluation, since the infection, which was a pre-existing condition, rendered the patient ineligible for all treatment assessments. Patient and disease characteristics for all 21 patients are summarized in Table 1.

MTD and overall toxicity

Of the 20 patients evaluated for MTD, six were treated in dose level 1, 11 in dose level 2 and three in dose level 3. MTD-defining DLT observed at each dose level is listed in Table 2. Two of the first three patients at dose level 3 developed DLT (grade 3 thrombocytopenia requiring dose omission), thus establishing the MTD at this dose level (gemcitabine 1000 mg/m^2 and IFN-α2b 7×10^6 IU). Five additional patients were then enrolled at the previous dose level (level 2), where two additional patients had

Table 1. baseline patient characteristics ($n=21$)

Median age [years (range)]	55 (29–71)
Male/female (%)	12 (57.1)/9 (42.9)
Karnofsky PS (%)	
100	11 (52.4)
90	5 (23.8)
80	4 (19.0)
60	1 (4.8)
Tumor type (%)	
pancreatic	3 (14.3)
ovarian	1 (4.8)
renal	10 (47.6)
NSCLC	7 (33.3)
American Joint Committee on Cancer disease stage (%)	
I	1 (4.8)
II	4 (19.0)
III	5 (23.8)
IV	9 (42.9)
unclear	2 (9.5)
Prior therapies (%)	
surgery	18 (85.7)
radiotherapy	5 (23.8)
chemotherapy	9 (42.9)
adjuvant	1 (4.8)
palliative	8 (38.1)
first-line	5 (23.8)
second-line	3 (14.3)
immunotherapy	3 (14.3)
none	2 (9.5)

DLT, for a total of three of 11 patients. Therefore, dose level 2 (gemcitabine 1000 mg/m^2 and IFN-α2b 5×10^6 IU) was considered the recommended regimen for phase II studies.

The median number of cycles completed per patient was 2 (range 0–5). Maximum WHO grade 3/4 hematologic and non-hematologic toxicities for these patients are presented by dose level in Table 3. The predominant hematologic toxicities were neutropenia and thrombocytopenia. Grade 3/4 thrombocytopenia, reported in five patients, did not result in hemorrhage or require platelet transfusions. Three of the seven patients with grade 4 neutropenia developed moderate neutropenic fever (two in cycle 1 and one in cycle 2) that did not require hospitalization or cause discontinuation from the study. Grade 3 non-hematologic toxicities included nausea/vomiting in five patients, and fever (neutropenic), elevated aminotransferase, alopecia and cardiotoxicity (heart failure) in one patient each. The only grade 4 non-hematologic toxicity, elevated ALT/AST, occurred in dose level 2 and met the criteria for DLT; this patient experienced moderate jaundice but did not require hospitalization. Four patients developed treatment-related flu-like symptoms that were mild and did not require hospitalization. No cutaneous or pulmonary toxicities were reported.

Ten patients discontinued the study due to adverse events considered related to study treatment. These included asthenia in three patients (coincided with flu syndrome in two patients), thrombocytopenia in two patients (both DLTs), and elevated creatinine, infection (pre-existing), abnormal kidney function, leukopenia and mucous membrane disorder in one patient each. An additional eight patients withdrew due to progressive disease and three at the patients' discretion.

Response

The best tumor responses of the 18 evaluable patients included: one (5.6%). patient with a partial response (with NSCLC), 10 (55.6%) patients with stable disease (eight with renal cancer and two with NSCLC) and six (33.3%) patients with disease progression (one with renal, two with pancreas and three with NSCLC). The response assessment of one

Table 2. MTD-defining toxicities (cycle 1)

Dose level	DLTs
1 ($n=6$): gemcitabine 500 mg/m^2 + IFN-α2b 5×10^6 IU	none
2 ($n=11$): gemcitabine 1000 mg/m^2 + IFN-α2b 5×10^6 IU	first six patients treated: sixth patient—thrombocytopenia grade 3 requiring dose omission in third week. last five patients treated: eighth patient—neutropenia grade 3 requiring dose reduction in the second week; 10th patient—thrombocytopenia grade 4 requiring dose reduction in second week and dose omission in third week; AST/ALT grade 4
3 ($n=3$): gemcitabine 1000 mg/m^2 + IFN-α2b 7×10^6 IU[a]	first patient—thrombocytopenia grade 3 requiring dose omission in third week; third patient—thrombocytopenia grade 3 requiring dose omission in second week

Table 3. Maximum WHO grades 3 and 4 toxicities by dose level ($n=20$[a])

Toxicity	Dose level 1: gemcitabine 500 mg/m^2 + IFN-α2b 5 × 10^6 IU ($n=6$)		Dose level 2: gemcitabine 1000 mg/m^2 + IFN-α2b 5 × 10^6 IU ($n=11$)		Dose level 3: gemcitabine 1000 mg/m^2 + IFN-α2b 7 × 10^6 IU ($n=3$)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	1	0	6	0	1	0
Neutropenia	2	1	3	5	1	1
Thrombocytopenia	0	0	2	1	2	0
Anemia	1	0	1	0	1	0
Nausea/vomiting	1	0	3	0	1	0
Fever (neutropenic)	0	0	1	0	0	0
ALT/AST	0	0	1	1	0	0
Alopecia	1	0	0	0	0	0
Cardiac	1	0	0	0	0	0

[a]One patient was not included in the MTD evaluation due to a pre-existing infection that caused discontinuation in cycle 1 (toxicities did not exceed grade 2).

patient was not done because of a lack of follow-up evaluations.

Discussion

In vitro experiments have demonstrated a strong activity of gemcitabine in human renal cell carcinoma cell lines, which is increased with the combined application of IFN-α.[21] On the basis of these results, we designed the present trial to establish the MTD and, thus, the recommended dose levels for gemcitabine and IFN-α2b for phase II trials. We included a variety of solid tumors in this trial based on those for which gemcitabine has proven antitumor activity.

The MTD-determining DLT of the combination was thrombocytopenia, which occurred at gemcitabine 1000 mg/m^2 and IFN-α2b 7 × 10^6 IU. Therefore, the recommended regimen for future phase II trials is 1000 mg/m^2 gemcitabine given once weekly plus 5 × 10^6 IU IFN-α2b given 3 × weekly, for 3 consecutive weeks every 28 days.

Hematologic toxicities, indicative of mylosuppession, were manageable with few clinical sequelae. Significant non-hematologic events reported in this study such as flu-like symptoms, hepatic and renal dysfunction (elevated AST/SLT and creatinine, respectively), gastrointestinal events (nausea/vomiting), central nervous system symptoms (asthenia), and cardiotoxicity were infrequent and commonly associated with IFN treatment.

Gemcitabine and IFN-α2b in combination may interact synergistically. IFN-α2b has been shown to enhance the growth inhibition caused by vinblastine or gemcitabine in human renal cell cancer xenografts in mice, with the gemcitabine combination showing superiority over the vinblastine combination.[22] In addition, the combination of IFN-α2b and cytosine arabinoside, a gemcitabine analog, has been widely used in humans to treat chronic myeloid leukemia, and has been shown superior to IFN alone.[24]

The actual mechanism by which IFN-α2b enhances the efficacy of gemcitabine, however, has not been clarified to date. It remains speculative that IFN-α2b may support the apoptosis induced by the cytotoxic agent. It is known, however, that IFN-α2b alone is capable of inducing apoptosis in human solid cancer cell lines.[25]

Of the 18 patients evaluable for response in this study, one (5.6%) patient with NSCLC had partial remission and 10 (55.6%) patients, of whom eight had renal cancer, reached stable disease. All patients had progressive disease upon entering the trial and most of them had more than one prior therapy (Table 1).

The activity of gemcitabine against NSCLC is well-established[2,3] and similar to that of other single-agent regimens, but its combination with platinum compounds has become the standard treatment for this tumor.[26] There is no accepted standard treatment for metastatic or advanced renal cell carcinoma. Neither IFN nor interleukin-2 nor combinations of these biological response modifiers with cytostatic agents has reached the position of a recommended standard therapy.

In human renal cell carcinoma, IFN-α2b monotherapy has produced response rates between 5 and 35%.[18] Gemcitabine alone has not been widely used for renal cell carcinoma, but one trial achieved a response rate of 8% and a stable disease rate of 48% in 37 evaluable patients.[27] The first study using the combination of gemcitabine and IFN-α2b in human renal cell carcinoma consisted of only nine patients

but confirmed the activity of the combination.[28] Although one patient achieved a minor remission and another reached stable disease, the median time to tumor progression (6.1 months) and survival (13.5 months) were favorable, and 43.5% of the progressive lesions did not continue to progress. The authors concluded the combination of gemcitabine and IFN demonstrated cytotoxic and cytostatic effects on metastases of renal cell carcinoma at a tolerable toxicity profile.

Conclusion

In this phase I study of gemcitabine combined with the immunotherapy, IFN-α2b, the recommended regimen for phase II trials is 1000 mg/m^2 gemcitabine given once weekly plus 5×10^6 IU IFN-α2b given $3 \times$ weekly, for 3 consecutive weeks every 28 days. Because increasing the duration of disease stabilization may prolong the survival of patients, these clinical results, particularly those in metastatic renal carcinoma, are encouraging and worthy of further evaluation in phase II trials. In addition, the prognosis of the patients in this study was poor (mostly stage III or IV disease), underscoring the potential for favorable results with manageable toxicity at the doses recommended in this study for phase II evaluation.

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