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Gemcitabine: once-weekly schedule active and better tolerated than twice-weekly schedule

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This paper reviews the toxicity profile of gemcitabine, a novel anticancer drug. Gemcitabine has been administered using two different treatment schedules: once weekly or twice weekly for 3 weeks followed by a week of rest (one cycle). It was well tolerated and alopecia was not a problem. Toxicity was greater in the twice-weekly schedule. Comparing the once-weekly with the twice-weekly schedule, WHO grade 3 or 4 thrombocytopenia was reported in 4.7 and 25.6% of patients, respectively. Other hematological toxicity was minimal. Transient WHO grade 3 or 4 elevations of ALT and AST occurred in 9.2 and 7.1% of patients, respectively, in the once-weekly schedule. For the twice-weekly schedule the corresponding percentages were 12.2 and 13.8%. Symptomatic toxicity was greater in patients who received twice-weekly gemcitabine. Nausea and vomiting was mild and generally well controlled without $5HT_3$ antagonists. However, there was a greater incidence of nausea and vomiting on the twice-weekly schedule. Flu-like symptoms were documented in 19.8% of patients receiving once-weekly and 63.3% of patients receiving twice-weekly gemcitabine. Peripheral edema, not related to cardiac, hepatic or renal failure, was seen more often in patients on twice-weekly treatment. As the efficacy of gemcitabine in non-small cell lung cancer was equivalent when using both regimens, the better tolerated and more easily administered once-weekly schedule is recommended.

Key words: Chemotherapy, efficacy, gemcitabine, NSCLC, safety.

Introduction

Gemcitabine is a novel nucleoside analog. It inhibits the cell processes required for DNA synthesis and repair and, in preclinical studies, it has demonstrated antitumor activity against a range of human tumor xenografts. These include lung, breast, head and neck, colon, and ovarian cancers.[1–7]

Preclinical studies indicated that toxicity with gemcitabine was likely to be schedule-dependent as well as dose-dependent. Animal toxicology studies showed that large doses given once per week were better tolerated than small daily doses which caused significant toxicity.

When gemcitabine was given daily (1–12 mg/m^2) as a 30 min infusion for 5 days every 3 weeks in phase I studies in humans, flu-like symptoms were the dose-limiting toxicity together with fever, malaise, headache and anorexia.[8] In some patients there were episodes of severe or life-threatening hypotension. Gemcitabine was better tolerated when a schedule of once every 2 weeks was used (data on file, Eli Lilly and Company). Doses of 3600 and 4560 mg/m^2 were reached using 4 h and 30 min infusions, respectively, but little efficacy was seen. The maximum tolerated dose (MTD) was 5700 mg/m^2 and myelosuppression was dose-limiting.

When given twice a week for 3 weeks, fatigue, fever, flu-like symptoms and skin rashes were reported.[9] There was reversible thrombocytopenia with a MTD of 65 mg/m^2 using a 30 min infusion period. When a 5 min infusion period was used the MTD increased to 150 mg/m^2 with thrombocytopenia and asthenia as dose-limiting toxicities.

The schedule for phase II studies that was finally chosen was supported by preclinical findings. As gemcitabine interferes with DNA synthesis, its biological activity depends upon intracellular nucleotide accumulation. *In vitro* using leukemia cells, saturation of this accumulation occurred at 10–20 μM gemcitabine.[10] In clinical studies these levels were only achieved with acceptable toxicity when a once-weekly schedule with a minimum dose of 300 mg/m^2/30 min was used.

A weekly schedule of gemcitabine administered as a 30 min infusion once weekly for 3 weeks followed by a week of rest provided efficacy with minimal non-hematological toxicity. The MTD was found to be 790 mg/m^2 in patients, most of whom had previously been treated with chemotherapy.[11] Thrombocytopenia was dose-limiting. In another

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study using the same schedule (data on file, Eli Lilly and Company), a MTD of 1370 mg/m^2 was established with myelosuppression as the principal toxicity. This trial was extended to look at duration of infusion and it was found that infusion times of 60 min and longer led to increasingly severe toxicity including bone marrow suppression and liver enzyme elevation. When gemcitabine was administered weekly to adult patients with advanced, relapsed acute leukemia at a constant infusion rate of 10 mg/m^2/min, the MTD was 4800 mg/m^2. The dose-limiting toxicity was non-hematological and included severe mucositis and skin rash (data file, Eli Lilly and Company).

Several phase II studies using gemcitabine as a single agent have been completed. Activity was observed in non-small cell lung cancer (NSCLC),[12–15] advanced pancreatic cancer,[16–17] previously treated epithelial ovarian cancer,[18] advanced breast cancer,[19] small cell lung cancer,[20] bladder cancer,[21] head and neck cancer,[22] and renal cancer.[23,24] In NSCLC, consistent response rates of around 20% have been recorded. These results are particularly promising as NSCLC is notoriously difficult to treat.[25] Existing therapies also give response rates of 5–20% when used as single agents but are often associated with significant toxicity. As previously described, gemcitabine was given once weekly at a starting dose of 800 mg/m^2. However, this dose was found to be too low in chemonaive patients and in later studies the dose was increased up to 1250 mg/m^2.

One phase II study was conducted in NSCLC using the twice-weekly schedule.[26] Ninety chemonaive patients received gemcitabine, starting dose 90 mg/m^2, twice weekly for 3 weeks followed by a week of rest (one cycle). A response rate of 19.7% was recorded which compares well with the weekly schedule.

In order to compare the safety profile of gemcitabine when used in these two different regimens, the safety data from all European and US trials using these regimens were studied. The inclusion and exclusion criteria for all these studies were similar, enabling direct integration and comparison. The integrated database for the once-weekly regimen included a total of 790 patients (who had received at least one dose of gemcitabine) from 18 studies in various solid tumors (Table 1). These data were compared with the 90 patients who received gemcitabine twice weekly, in the above-mentioned NSCLC study.

The safety profile was assessed using WHO toxicity gradings and the WHO grades reported in these gemcitabine studies are the maximum reported at any time for the patient on study and therefore represent a fairly rigorous criterion for assessment (Tables 2 and 3).

In all studies laboratory toxicity was recorded irrespective of drug causality and results for all 790 patients receiving the once-weekly regimen and for all 90 patients receiving the twice-weekly regimen are reported.

Hematology

Platelets

The most significant difference between the two treatment groups was in platelet toxicity (Table 2). WHO grade 3 and 4 thrombocytopenia was recorded in 3.7 and 1.0% of patients receiving the once-weekly schedule, and in only three of the 790 patients (0.4%) was treatment discontinued. With the twice-weekly schedule, platelet toxicity was more significant. Twenty-three patients (25.6%) experienced grade 3 or 4 toxicities which resulted in 6.8% (123/1797) of doses being reduced or omitted. Thrombocytopenia was reported as serious in four patients, but no patients were discontinued because of thrombocytopenia.

Hemoglobin

Anemia was not a significant problem in the once-weekly treatment group (Table 2). Of the 790 patients receiving gemcitabine weekly, WHO grade 3 and 4 anemia was reported in 6.4 and 0.9% of patients, respectively. Only two patients (0.3%) discontinued treatment due to anemia and, in general, it was managed with the use of conventional transfusions which were required in 19% of patients. With the twice-weekly schedule, no grade 4 toxicity occurred. However, 26.7 and 2.2% of patients experienced grade 2 and grade 3 toxicity, respectively, and 58.9% of patients required transfusions.

Leukocytes and neutrophils

WHO grade 3 and 4 leukocyte toxicity was recorded in 8.1 and 0.5%, respectively, of the patients who received the once-weekly schedule of gemcitabine (Table 2). Leukopenia was rarely dose-limiting and only one patient (0.1%) discontinued treatment. WHO grade 3 and 4 segmented neutrophil toxicity

Table 1. Summary of gemcitabine studies used for the integrated analysis: once-weekly schedule

Study number	Indication	Previous chemotherapy	Starting dose (mg/m^2;
E003[18]	breast	yes/no	800
E004[11]	NSCLC	no	800/1000
E005[a]	colorectal	no	1000
E007[17]	ovary	yes	800
E010[22]	renal	no	800
E012[16]	pancreas	no	1000
E018[12]	NSCLC	no	1250
JHAE[13]	NSCLC	no	800
JHAF[27]	colorectal	no	800
JHAG[a]	prostate	no	800
JHAH[a]	melanoma	no	800/1000
JHAI[a]	breast	yes	800
JHAJ[a]	ovary	yes	800
JHAK[28]	gastric	no	800/1000
JHAL[16]	pancreas	no	800
JHAN[23]	renal	no	800
JHAO[19]	SCLC	no	1000/1250
JHAX[14]	NSCLC	no	1000/1250

[a] Data on file, Eli Lilly and Company.

Table 2. Summary of maximum WHO grades for laboratory toxicity: once-weekly schedule (1 × w) $n=790$, twice-weekly schedule (2 × w) $n=90$

	Maximum WHO grades (% of patients)									
	0		1		2		3		4	
	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w
Hematological										
hemoglobin	34.4	10.0	38.9	61.1	19.3	26.7	6.4	2.2	0.9	0
white blood cells	38.9	27.8	24.8	21.1	27.7	30.0	8.1	21.1	0.5	0
segmented neutrophils[a]	36.2	44.9	17.2	22.5	22.2	19.1	18.7	11.2	5.7	2.2
platelets	79.1	46.7	9.9	15.6	6.3	12.2	3.7	18.9	1.0	6.7
Liver										
ALT	32.4	28.8	37.4	22.7	21.0	27.3	7.4	19.7	1.8	1.5
AST	35.6	29.3	39.1	25.9	18.2	31.0	5.7	12.1	1.4	1.7
alkaline phosphatase	49.6	43.8	29.0	43.8	14.8	7.9	4.5	4.5	2.1	0
bilirubin	89.8	89.9	7.2	9.0	1.4	0	1.0	1.1	0.5	0
Renal										
BUN	82.8	93.2	15.0	6.8	2.2	0	0	0	0	0
creatinine	91.9	96.6	7.5	3.4	0.5	0	0.1	0	0	0

[a] Segmented neutrophils have been converted to WHO scores using granulocyte criteria

was 18.7 and 5.7%, respectively. The incidence of infection associated with this level of neutropenia was low (grades 2 and above infections were reported in only 9.5% of patients). Of the patients receiving the twice-weekly schedule, WHO grade 3 leukopenia was experienced by 21.1% of patients and there was no grade 4 toxicity. However, two cases (2.2%) of grade 4 neutropenia were reported. The clinical relevance of these grade 3 and 4 toxicities was difficult to assess but clinical infections were reported in only 3.3% of patients.

Liver toxicity

Differences in toxicity between the two treatment schedules were observed for liver toxicity (Table 2). For the once-weekly schedule, WHO grade 3 and 4

Table 3. Summary of maximum WHO toxicity grades for symptomatic toxicity: once-weekly schedule (1 × w) $n=439$, twice-weekly schedule (2 × w) $n=90$

	Maximum WHO grade (% of patients)									
	0		1		2		3		4	
	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w	1 × w	2 × w
Allergic	96.1	97.8	3.2	2.2	0.5	0	0.2	0	0	0
Constipation	93.6	94.4	5.3	5.6	0.9	0	0.2	0	0	0
Cutaneous	74.3	60.0	16.1	16.7	9.4	23.3	0.2	0	0	0
Diarrhea	92.4	90.0	4.4	10.0	2.8	0	0.5	0	0	0
Fever	60.5	63.3	21.8	23.3	17.0	10.0	0.7	3.3	0	0
Cardiac function	98.2	100	0.9	0	0	0	0.7	0	0.2	0
Hair	86.7	92.2	9.0	6.7	3.9	1.1	0.5	0	0	0
Hematuria	63.4	68.6	32.4	29.1	4.2	2.3	0	0	0	0
Infection	91.0	96.7	6.2	1.1	1.6	2.2	0.9	0	0.2	0
Nausea/vomiting	34.7	33.3	26.9	22.2	17.7	10.0	19.8	34.4	0.9	0
Oral	93.1	84.4	4.4	13.3	2.3	1.1	0.2	1.1	0	0
Pain	82.3	76.7	10.6	12.2	6.0	10.0	1.1	1.1	0	0
Pericarditis	99.8	100	0.2	0	0	0	0	0	0	0
Peripheral neurotoxicity	96.6	97.8	3.2	2.2	0.2	0	0	0	0	0
Proteinuria	61.8	26.7	35.1	66.3	2.7	7.0	0.4	0	0	0
Pulmonary	91.7	81.1	4.8	11.1	1.6	5.6	1.6	2.2	0.2	0
Cardiac rhythm	97.7	100	1.4	0	0.7	0	0.2	0	0	0
State of consciousness	89.9	100	5.3	0	4.4	0	0.5	0	0	0

toxicity was as follows: ALT 7.4 and 1.8%; AST 5.7 and 1.4%; alkaline phosphatase 4.5 and 2.1%; bilirubin 1.0 and 0.5%. In most cases the elevation of the enzymes was transient, asymptomatic and rapidly reversible, and only four of 790 patients discontinued treatment because of abnormalities of liver function tests (0.5%). A further patient who had a long history of chronic alcoholism was discontinued due to liver failure. Liver toxicity was more pronounced in the patients receiving gemcitabine twice weekly. Approximately 30% of patients had normal enzymes throughout the study and approximately 90% of patients had normal bilirubin levels. There was no grade 4 bilirubin toxicity. Fourteen patients (21.2%) had an ALT of grade 3 or 4 and eight patients (13.8%) had an AST of grade 3 or 4. In most patients toxicity was mild (grade 1 or 2) and of no apparent clinical relevance. It should also be noted that at study entry 10.3 and 13.1% of patients in the once-weekly group and 5.4 and 3.8% of patients in the twice-weekly group had abnormal ALT and AST values (WHO grade 1 or greater).

Renal toxicity

In patients receiving the once-weekly schedule, WHO grade 3 toxicity for BUN and creatinine was 0 and 0.1%, respectively. No WHO grade 4 toxicity was recorded. Mild proteinuria and hematuria were commonly reported but these were rarely clinically significant. (These parameters are included in Table 3 as they were assessed for causality.) However, a few cases of renal failure of uncertain etiology were reported. Three patients experienced renal failure while on gemcitabine therapy but recovered after being withdrawn from the study. Two of these patients were diagnosed as having hemolytic uremic syndrome. Two further patients experienced renal failure some time after discontinuation from the study.

With the twice-weekly schedule, normal creatinine levels were reported in 96.6% of patients and 93.2% of patients had normal urea levels (some centers tested creatinine and not urea). There were no grade 3 or 4 toxicities. Three patients were withdrawn because of CrEDTA and two because of decreased creatinine clearance. However, serum creatinine levels and urea remained normal in all cases. The incidence of microscopic hematuria was higher in the twice-weekly group (WHO grade 1 hematuria, 66.3 versus 35.1% in the once-weekly group) but there were no associated discontinuations of treatment. Mild proteinuria was also frequently reported but the incidence was similar to that of the once-weekly group.

Therefore, although renal toxicity is not a significant problem, clinicians should be aware that renal failure of uncertain aetiology may occur during treatment with gemcitabine.

Symptomatic toxicity

For the studies using gemcitabine weekly, non-laboratory toxicity data are reported for a total of 439 patients. In these studies, the investigators assessed the causality of any adverse events; whereas, in other studies, investigators used the WHO toxicity rating scale for all events regardless of causality. For the study using gemcitabine twice weekly, WHO grades for symptomatic toxicity where considered related to treatment were recorded for all 90 patients.

For symptomatic toxicity, the main difference observed between the two treatment schedules was an increased incidence of nausea and vomiting among patients receiving gemcitabine twice weekly (Table 3). WHO grade 3 (vomiting requiring therapy) and grade 4 (intractable vomiting) was recorded in 19.8 and 0.9% of patients receiving gemcitabine once weekly. Although no grade 4 nausea and vomiting was recorded, 31 patients (34.4%) experienced grade 3 toxicity in the twice-weekly treatment group. However, in both groups, nausea and vomiting was rarely dose-limiting and rarely resulted in discontinuation of treatment (0.9 and 0% of patients in the once-weekly and twice-weekly groups, respectively). Nausea and vomiting was well controlled with standard antiemetics and 5-HT_3 antiemetics were usually not required.

In addition, somnolence was reported as an adverse event irrespective of causality in only 13.5% of patients who received gemcitabine once weekly but in 25.6% of patients receiving gemcitabine twice weekly (Table 3). However, a WHO grade was not allocated for 'state of consciousness' in any of the cases reported in the twice-weekly study.

Slightly more moderate WHO cutaneous toxicity was reported with the twice-weekly schedule (Table 3). This is corroborated by the fact that a mild rash was reported, irrespective of causality, in 40% of patients in the twice-weekly treatment group compared with 21.5% in the once-weekly group. Alopecia was not found to be a problem in patients receiving gemcitabine treatment with most patients not having any hair loss. There was no difference between the two treatment groups.

No other significant differences in symptomatic toxicity were observed between the two treatment groups.

Adverse events not covered by the WHO toxicity gradings

Certain events are not covered by the WHO grading system and were recorded separately. They are reported irrespective of causality.

Flu-like symptoms

Flu-like symptoms (including headache, back pain, chills, myalgia, asthenia and anorexia) have been reported during treatment with gemcitabine. These were usually mild, of brief duration and rarely dose-limiting. The mechanism of this event is unknown but some investigators have reported that symptoms can be relieved with paracetamol. A total of 155 out of the 790 patients in the once-weekly studies (19.6%) reported flu-like symptoms but only one patient (0.1%) discontinued treatment due to this side effect. Flu-like symptoms were reported in 63.3% of patients in the twice-weekly study and, although none of these occurrences were reported as serious, this was considered by investigators to be the most significant toxicity with the twice-weekly schedule.

Edema

Edema or peripheral edema were reported in 18.1 and 12.9% of patients receiving the once-weekly regimen, respectively. When all types of edema are considered (edema, peripheral edema and face edema), 28.4% of patients in the once-weekly studies reported this event, and this was classified as mild in 13.5%, moderate in 12.1% and severe in 2.6% of patients. In six of 790 patients (0.8%) treatment was discontinued due to edema. Edema and peripheral edema were reported in 31.1 and 25.6% of patients, respectively, in the twice-weekly study but only one patient (1.1%) was discontinued because of this adverse event. The mechanism of the edema is unknown, but it is not associated with any evidence of cardiac, hepatic or renal failure.

Dose intensification

From these results, it is apparent that the twice-weekly schedule resulted in more toxicity than the

once-weekly schedule. More than 50% of doses were reduced or omitted (589 reduced and 321 omitted doses out of a total of 1797 protocol-defined doses) when using this schedule. As a comparison, in a 161 patient NSCLC study using the once-weekly schedule, less than 10% of doses were either reduced or omitted (75 reduced and 103 omitted doses out of a total of 1711 protocol defined doses). Moreover, 16 out of the 90 patients (17.8%) receiving gemcitabine twice weekly were withdrawn due to an adverse event (irrespective of drug causality) compared with 88 out of the 790 patients (11.1%) receiving gemcitabine once weekly.

Conclusions

It is unusual to see such a mild side effect profile in an active cytotoxic agent. When given once weekly, there is in particular a low incidence of the adverse events usually associated with cytotoxic drugs, i.e. myelosuppression, nausea and vomiting, and alopecia. However, some adverse events occurred with a higher incidence than with standard cytotoxic treatments. Flu-like symptoms were commonly reported, although these were mild, short-lasting, rarely dose-limiting and often relieved by paracetamol. Edema was reported in a number of patients but caused few discontinuations of treatment.

The integrated safety data demonstrated that gemcitabine has a good safety profile when administered once a week for 3 weeks followed by a week of rest. Although, the twice-weekly schedule was as efficacious as the once-weekly schedule, it caused a greater degree of toxicity which resulted in more patients receiving this schedule having doses reduced or omitted than with the once-weekly schedule.

A further attraction of the once-weekly schedule is that patients only need to attend the clinic once a week. This advantage is lost when the twice-weekly schedule is used.

In conclusion, the once-weekly schedule of gemcitabine should be used in preference to the twice-weekly schedule. Gemcitabine 800–1250 mg/m^2, when administered once a week for 3 weeks followed by a week of rest (one cycle), is well tolerated.

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