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Safety profile of gemcitabine

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This paper reviews the toxicity profile of gemcitabine in a large group of patients (up to 790) from pivotal phase II studies, in which the drug was given intravenously as a 30 min infusion, in a schedule once a week for 3 weeks followed by a week of rest. The safety profile of gemcitabine is unusually mild for such an active agent in solid tumours. Haematological toxicity is mild and short-lived with modest WHO grades 3 and 4 for haemoglobin (6.4% and 0.9% of patients), leukocytes (8.1% and 0.5%), neutrophils (18.7% and 5.7%) and platelets (6.4% and 0.9%). The incidence of grade 3 and 4 infection associated with this level of myelosuppression was low (0.9% and 0.2%). Transaminase elevations occurred frequently, but they were usually mild, and rarely dose limiting. Mild proteinuria and haematuria were seen but were rarely clinically significant. There was no evidence of cumulative hepatic or renal toxicity. Nausea and vomiting was mild, rarely dose limiting, and generally well controlled with standard antiemetics. Flu-like symptoms were experienced in a small proportion of patients but were of short duration. Where oedema/peripheral oedema was experienced there was no evidence of any association with cardiac, hepatic or renal failure. Hair loss was rare, with WHO grade 3 alopecia reported in 0.5% of patients. There was no grade 4 alopecia. Furthermore, gemcitabine displayed minimal toxicity in elderly patients, and the side-effect profile does not seem to be affected by patient age. The adverse events typically experienced with cytotoxic agents, namely myelosuppression, nausea and vomiting and alopecia, are not seen to such a degree with gemcitabine, and this non-overlapping toxicity profile suggests that gemcitabine is a promising agent for incorporation into combination chemotherapy regimens.

Introduction

Gemcitabine is a novel nucleoside analogue with activity across a broad range of solid tumours including non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, pancreas cancer and small-cell lung cancer.[1] Its activity is thought to be due to a unique series of mechanisms that potentiate the activity of the gemcitabine nucleotide, which is then incorporated into the DNA chain in a way which makes it less susceptible to detection and excision repair by "proof-reading" exonuclease enzymes (a process termed "masked DNA chain termination").[1,2]

In phase I studies the toxicity of gemcitabine was shown to be schedule dependent.[1,3–5] Four dosing schedules were evaluated. In the two schedules in which the drug was given more frequently, non-haematological toxicity was a problem: fever, flu-like symptoms, and severe hypotension with the daily × 5 q3W schedule;[3] fatigue, fever, flu-like symptoms and skin rash with the twice a week × 6 q4W schedule.[4] Using a once every 2 weeks schedule gemcitabine was well tolerated,[5] but preclinical and phase I data suggest superiority for more frequent administration.[6] A weekly schedule for 3 weeks followed by a week of rest provided activity with minimal non-haematological toxicity and the maximum tolerated dose (MTD) identified in previously treated patients was 790 mg/m^2, with myelotoxicity (thrombocytopenia) being the dose-limiting factor.[7] Based on the phase I data, this schedule was the one adopted for the early phase II studies.[8,9] More recent phase I trials, again using a weekly schedule, have examined dose escalation in previously untreated patients, the MTD in the range 2800–3500 mg/m^2, with dose-limiting toxicity being neutropenia and, in the MD Anderson study, reversible transaminase elevation.[10]

This review summarizes the safety data for the phase II studies in which gemcitabine was administered as a 30 min infusion, once a week for 3 weeks followed by a week of rest, at starting doses in the range 800–1250 mg/m^2. The source of this data is the "Gemcitabine Safety Summary" section of the *Gemcitabine European Community Registra-*

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Table 1. Maximum WHO grades for laboratory toxicity (% of patients) [a]

	No. patients	WHO grades				
		0	1	2	3	4
Haematological						
Haemoglobin	781	34.4	38.9	19.3	6.4	0.9
Leukocytes	781	38.9	24.8	27.7	8.1	0.5
Neutrophils [b]	766	36.2	17.2	22.2	18.7	5.7
Platelets	781	79.1	9.9	6.3	3.7	1.0
Liver						
Alanine transaminase	620	32.4	37.4	21.0	7.4	1.8
Aspartate transaminase	736	35.6	39.1	18.2	5.7	1.4
Alkaline phosphatase	776	49.6	29.0	14.8	4.5	2.1
Bilirubin	773	89.8	7.2	1.4	1.0	0.5
Renal						
Blood urea nitrogen	720	82.8	15.0	2.2	0	0
Creatinine	777	91.9	7.5	0.5	0.1	0
Proteinuria	748	41.4	46.9	11.1	0.5	0
Haematuria [c]	746	– [c]	– [c]	– [c]	– [c]	– [c]

[a] Patients on therapy = 790. [b] Segmented neutrophils were converted to WHO scores using granulocyte count criteria. [c] Haematuria was not WHO graded. The dipstick methodology was used: grade 0 = nil (57.6% of patients); grade 1 = + (21.4%); grade 2 = ++ or +++ (19.6%); grade 3 = ++++ (1.3%).

tion Dossier. The WHO grades reported represent the maximum experienced at any point in therapy, and constitute the most severe toxicity even if that grade occurred only once during all courses of the drug received.

WHO laboratory toxicity

WHO grades were allocated irrespective of causality. WHO laboratory toxicity is reported for 790 patients on therapy (Table 1).

Haemoglobin

WHO grade 3 and 4 toxicity was reported in 6.4% and 0.9% of patients, respectively. In only 2 of 790 patients (0.3%) was treatment discontinued due to anaemia. There was no evidence of cumulative toxicity in the later cycles of gemcitabine treatment. Overall, anaemia was not considered to be a significant problem and was manageable with the use of conventional transfusions, which were required in 19% of patients.

Leukocytes and granulocytes

WHO grade 3 and 4 leukocyte toxicity was recorded in 8.1% and 0.5% of patients, respectively. In only 1 of 790 patients (0.1%) was treatment discontinued due to leukopenia. Previous exposure to cytotoxic chemotherapy appeared to increase the frequency and severity of leukopenia caused by gemcitabine, although even in previously treated patients leukopenia was rarely dose limiting. Counts of segmented neutrophils, a more sensitive indicator of toxicity than the white blood cell count, were converted to WHO toxicity scores using criteria for granulocyte toxicity. WHO grade 3 and 4 segmented neutrophil toxicity was 18.7% and 5.7%. The incidence of infection associated with this level of neutropenia was low (grades 2 and above infections were reported in only 1.6% and 1.3% of chemo-naive and pretreated patients, respectively). There was no evidence of cumulative toxicity.

Platelets

WHO grade 3 and 4 toxicity was recorded in only 3.7% and 1.0% of patients. In only 3 of 790 patients (0.4%) was treatment discontinued due to thrombocytopenia. There was no evidence of cumulative toxicity. Patients previously treated with cytotoxic chemotherapy tended to show more pronounced platelet toxicity. There appeared to be no difference in toxicity between patients starting at the 800, 1000 and 1250 mg/m^2 dose levels.

Alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, bilirubin

WHO grade 3 and 4 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%. The toxicity was manifest as a transient, asymptomatic, rapidly reversible elevation of the enzymes. In only 4 of 790 patients (0.5%) was treatment discontinued due to abnormalities in liver function. Another patient who had a long history of chronic alcoholism was discontinued due to liver failure. There was no increase in the median of distribution of maximum values across cycles for alkaline phosphatase or bilirubin. Levels of transaminases did not increase beyond cycles 1 and 2, suggesting that there is no cumulative toxicity.

Blood urea nitrogen (BUN), creatinine, proteinuria, haematuria

WHO grade 3 toxicity for BUN, creatinine and proteinuria was respectively 0%, 0.1% and 0.5%. No WHO grade 4 toxicity was recorded. Haematuria was not WHO graded; instead the dipstick methodology was used (Table 1). Overall, mild proteinuria and haematuria were commonly reported but these were rarely clinically significant. Renal toxicity as assessed by BUN and serum creatinine was not a significant problem.

However, a few cases of renal failure of uncertain aetiology were reported. Three patients experienced renal failure while on gemcitabine therapy. In one case WHO grade 3 creatinine and grade 1 proteinuria and haematuria as well as hyperuricaemia were reported after 4 cycles of treatment. Treatment was discontinued and the patient had normal renal function 10 days later. One patient was withdrawn from the study after 13 cycles due to progressive renal dysfunction. Renal biopsy indicated thrombotic microangiopathy that was possibly drug related. The third patient discontinued treatment after 5 cycles because of acute kidney failure associated with platelet and haemoglobin toxicity. The patient recovered after being withdrawn from the study. In retrospect, the investigator thought that this event might have been a manifestation of haemolytic uraemic syndrome.

Two patients experienced renal failure some time after discontinuation from the study. In one case it was not possible to ascertain whether the renal failure, which occurred 2 weeks after discontinuation from the study, was due to sepsis or possibly related to gemcitabine treatment. The patient began peritoneal dialysis but died within 1 week from severe infection and acute renal failure. In the second case, evidence of renal failure developed with signs of haemolysis 25 days after discontinuation from the study. The renal failure necessitated dialysis. Review of laboratory data and a kidney biopsy suggested possible microangiopathic anaemia. One can conclude that although renal toxicity is not a significant problem, there have been a few reports of renal failure of uncertain aetiology and clinicians should be aware that this may be a rare side effect of gemcitabine therapy.

WHO symptomatic toxicity

WHO grades were allocated if adverse events were possibly drug related. WHO symptomatic toxicities are reported for a subset of 439 patients (Table 2).

Nausea and vomiting

WHO grade 3 and 4 was recorded in 19.8% and 0.9% of patients. In only 0.9% of patients was treatment discontinued due to nausea and vomiting. Overall, nausea and vomiting required therapy in about 20% of patients, was rarely dose limiting and was easily manageable with standard antiemetics; 5-HT_3 antiemetics were not usually required. This is important since nausea and vomiting is a worrying toxicity of many cytotoxic regimens, causing psychological and physical distress which, if severe, warrants rehydration which may in turn require hospitalization.

Oral toxicity

WHO grade 3 and 4 toxicity was 0.2% and 0%. In only 1 of 439 patients was treatment discontinued due to oral toxicity.

Diarrhoea

WHO grade 3 and 4 toxicity was 0.5% and 0% and in no patient was treatment discontinued due to diarrhoea.

Pulmonary toxicity

WHO grade 3 and 4 toxicity was 1.6% and 0.2%, respectively. Although possibly drug-related dyspnoea was commonly reported, it was usually mild and rarely required specific therapy. Whether dyspnoea is actually related to the administration of gemcitabine or to underlying cardiac or pulmonary dysfunction is still unclear. For most of these patients, alternative aetiologies were identified, e.g.

Table 2. Maximum WHO grades for symptomatic toxicity (% of patients) [a]

	No. patients	WHO grades				
		0	1	2	3	4
Nausea/vomiting	435	34.7	26.9	17.7	19.8 [b]	0.9
Oral	435	93.1	4.4	2.3	0.2	0
Diarrhoea	435	92.4	4.4	2.8	0.5	0
Pulmonary	435	91.7	4.8	1.6	1.6	0.2
Fever	435	60.5	21.8	17.0	0.7	0
Allergic	435	96.1	3.2	0.5	0.2	0
Cutaneous	435	74.3	16.1	9.4	0.2	0
Hair	435	86.7	9.0	3.9	0.5	0
Infection	435	91.0	6.2	1.6	0.9	0.2
Cardiac rhythm	435	97.7	1.4	0.7	0.2	0
Cardiac function	435	98.2	0.9	0	0.7	0.2
Pericarditis	435	99.8	0.2	0	0	0
State of consciousness	435	89.9	5.3	4.4	0.5	0
Peripheral neurotoxicity	435	96.6	3.2	0.2	0	0
Constipation	435	93.6	5.3	0.9	0.2	0
Pain	435	82.3	10.6	6.0	1.1	0
Haemorrhage	160	98.1	0.6	1.3	0	0

[a] Patients on therapy = 439. [b] Generally controlled with standard antiemetics.

pleural effusions, pneumonia, atelectasis, and pericardial effusions.

Fever

WHO grade 3 and 4 fever was 0.7% and 0%. Fever was frequently associated with other flu-like symptoms which will be discussed later. Fever was usually mild, of brief duration, easily manageable, rarely dose limiting, and rarely related to infection.

Allergic toxicity

Three patients (0.7%) reported bronchospasm (WHO grade 2 or 3) including one case of grade 3 toxicity (bronchospasm requiring parenteral therapy), which was successfully treated with bronchodilators and steroids. Another patient known to have chronic obstructive lung disease experienced bronchospasm after two injections of gemcitabine and died the day after from respiratory insufficiency. In any case, clinicians should be aware of the possibility of bronchospasm developing shortly after the administration of gemcitabine.

Cutaneous toxicity

WHO grade 3 and 4 toxicity was 0.2% and 0%. A transient, mild erythematous pruritic rash was frequently reported; it sometimes subsided with local therapy despite continuation of therapy. Desquamation was observed on at least one occasion. In only 2 of 439 patients was treatment discontinued due to cutaneous toxicity. There were no reports of injection site necrosis.

Hair toxicity

WHO grade 3 and 4 toxicity was 0.5% and 0%. Overall, there was little hair toxicity, and 86.7% of patients had no hair loss at all. Alopecia is one of the most distressing side effects of cytotoxic therapy, and it is encouraging to see an active cytotoxic agent which produces no or minimal hair loss.

Infection toxicity

WHO grade 3 and 4 toxicity was 0.9% and 0.2%. In only 2 patients was treatment discontinued due to severe infection associated with leukopenia. Neither the starting dose (800–1250 mg/m^2 dose range) nor the previous chemotherapy status of the patient had an effect on either the frequency or the severity of the episodes of infection. Overall, drug-related infection was usually mild, rarely dose limiting and easily manageable.

Cardiac rhythm, cardiac function, pericarditis

WHO grade 3 and 4 toxicity was as follows: cardiac

rhythm, 0.2% and 0%; cardiac function, 0.7% and 0.2%; pericarditis, 0% and 0%. Overall, there is no evidence that gemcitabine causes cardiac toxicity.

State of consciousness

WHO grade 3 and 4 toxicity was 0.5% and 0%. Overall, somnolence thought to be possibly drug related was reported for 10.2% of patients, but was usually mild or moderate. Asthenia was also commonly reported, but the incidence of asthenia is confounded by the natural history of the underlying disease.

Peripheral neurotoxicity, constipation

There was no WHO grade 3 or 4 peripheral neurotoxicity. WHO grade 1 and 2 peripheral neurotoxicity was 3.2% and 0.2%, respectively. WHO grade 3 and 4 constipation was 0.2% and 0%.

Adverse events not covered by the WHO toxicity gradings

Certain events are not covered by the WHO grading system and were recorded separately. These are summarized for 790 patients on therapy. Adverse events were reported irrespective of causality.

Flu-like symptoms

The total number of patients with flu-like symptoms was 155 (19.6%). These symptoms when reported were usually mild (12.6%) or moderate (5.4%) and were rarely severe (1.5%), with only 1 patient (0.1%) discontinued due to this side effect. Headache, back pain, chills, myalgia, asthenia, and anorexia were the most commonly reported symptoms. Asthenia was commonly considered to be drug related even when reported as an isolated symptom. Cough, rhinitis, malaise, sweating and insomnia were also reported. Flu-like symptoms might also have accounted for some, but not all, cases of fever. The flu-like symptoms were usually mild, of brief duration and rarely dose limiting. The mechanism of this event is unknown. Investigators have reported that symptoms can be relieved with paracetamol.

Oedema

Oedema or peripheral oedema was seen in 28.4% of patients, and was classified as mild in 13.5%, moderate in 12.1% and severe in 2.6% of patients. In 6 of 790 patients (0.8%) treatment was discontinued due to oedema. Oedema is not associated with any evidence of cardiac, hepatic or renal failure; the mechanism remains unknown.

Toxicity profile unaffected by patient age

The gemcitabine database was also analysed to identify any influence of age on the toxicity profile.[11] The patient population was divided into two groups: patients less than 65 years of age (n = 549) and patients aged 65 years or older (n = 241). This age of 65 years is the recommended age cut-off in the "Final Agreed Tripartite Guideline — Studies in Support of Special Population: Geriatrics" of the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*. Toxicity did not differ significantly between younger and older patients, with the exception of nausea and vomiting which was lower in the older age group. A difference was also noted in the incidence of peripheral oedema (15.3% in patients less than 65 years vs 25.3% in older patients), which may possibly have been due to the generally higher incidence of peripheral oedema in the elderly. Furthermore, a separate analysis on 331 patients with NSCLC showed that response rate was not affected by patient age.

Conclusions

Overall, the safety data demonstrate that gemcitabine has a favourable side-effect profile. Interestingly for such an active agent in solid tumours, gemcitabine produces a low incidence of adverse events usually associated with cytotoxic drugs, namely myelosuppression, nausea, vomiting and alopecia (Table 3). Myelosuppression with gemcitabine typically does not require hospitalization or treatment with colony stimulating factors, and nausea/vomiting generally does not require hospitalization for rehydration or treatment with the more powerful 5-HT_3 antiemetics. The low incidence and severity of side effects with gemcitabine suggests that the costs associated with managing these adverse events may be expected to be lower than with many other cytotoxic agents. This non-overlapping toxicity makes the drug an attractive candidate for trial in combination with other cytotoxic agents. Furthermore, gemcitabine has minimal toxicity in elderly patients and the side effects do not seem to be affected by patient

Table 3. Gemcitabine toxicity profile compared with that of major antineoplastic agents

Class	Acute toxicity			Other toxicity
	Leukocyte	Platelet	Nausea/Vomiting	
Plant derivatives				
Vinblastine	Marked	Marked	Mild	Mucositis
Etoposide	Moderate	Mild	Mild	Distal neuropathy
Antibiotics				
Doxorubicin	Marked	Marked	Moderate	Alopecia, cardiomyopathy
Mitomycin C	Marked	Marked	Moderate	Renal, pulmonary
Alkylating agents				
Cyclophosphamide	Marked	Mild	Moderate	Cystitis, alopecia
Ifosfamide	Moderate	Moderate	Mild	Neurotoxicity, cystitis
Cisplatin	Moderate	Moderate	Severe	Renal failure, ototoxicity, neurotoxicity
Gemcitabine	Mild	Mild	Mild	Flu-like symptoms, oedema

Modified from BA Chabner. Anticancer Drugs. In: De Vita VT, ed. *Cancer: Principles & Practice of Oncology*, 4th edn. 1993, 325–9.

age. In summary, gemcitabine is a new drug with an unusually mild toxicity profile and high activity that will play an important role in future strategies for the treatment of solid tumours.

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