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Review paper

Gemcitabine—a safety review

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Gemcitabine is a novel nucleoside analog with demonstrated efficacy across a range of solid tumors. This paper reviews the single-agent safety profiles of 979 patients in 22 completed clinical studies using a day 1, 8, 15 q 28 day, 800–1250 mg/m^2 dose schedule. Hematological toxicity was mild with WHO grade 3 and 4 toxicities recorded for hemoglobin (6.8 and 1.3% of patients), leukocytes (8.6 and 0.7%), neutrophils (19.3 and 6.0%) and platelets (4.1 and 1.1%). Myelosuppression was short lived and rarely of clinical significance. Mucositis and alopecia were rare, and nausea and vomiting mild. Transient rises in transaminases, mild proteinuria and hematuria were common, but rarely clinically significant. Renal failure of uncertain etiology was reported in seven instances. Some patients (18.9%) experienced transient flu-like symptoms and mild fever was reported in 37.3% of flu patients. Peripheral edema was reported in 20.3% of patients in the absence of cardiac, hepatic or renal failure. Thus, gemcitabine is well tolerated and has a mild toxicity profile. Of nearly 11 000 protocol-defined injections, 94% were administered and only 14% were reduced. Grade 3 or 4 non-laboratory toxicities with a frequency of more than 1% were only seen for infection (1.2%), nausea and vomiting (18.4%), and pulmonary toxicity (1.4%). [© 1998 Rapid Science Ltd.]

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Introduction

All cytotoxic drugs have side effects. These commonly occur at therapeutic dosages and may be severe enough to result in reduction of dose or even discontinuation of treatment. Side effects may occur immediately after the start of treatment or may become apparent after several weeks or months of treatment.

The nucleoside analog gemcitabine is a novel anticancer drug. Preclinical studies indicated that toxicity with gemcitabine was likely to be schedule dependent. It was found that large doses given once per week were better tolerated than small daily doses. This was a key observation that correctly predicted the effects observed in subsequent phase I and II clinical trials.

In phase I studies in humans, when gemcitabine was given daily (1–12 mg/m^2) for 5 days every 3 weeks, flu-like symptoms were the dose-limiting toxicity together with fever, malaise, headache and anorexia.[1] In some patients at doses of 7 mg/m^2 or higher there were episodes of severe or life-threatening hypotension. Gemcitabine was better tolerated when a schedule of once every 2 weeks was used.[2] The dose-limiting toxicity was myelosuppression, predominantly thrombocytopenia, and the maximum tolerated dose (MTD) was 5700 mg/m^2, with no significant clinical anti-tumor activity.

When given twice a week for 3 weeks, fatigue, fever, flu-like symptoms and skin rashes were reported.[3] There was also reversible thrombocytopenia with a MTD of 65–75 mg/m^2 using a 30 min infusion period.

A weekly schedule for 3 weeks followed by 1 week of rest provided efficacy with minimal non-hematological toxicity and the MTD was found to be 790 mg/m^2 in patients who had previously been treated with chemotherapy.[4] Thrombocytopenia was dose limiting. In another study using the same schedule,[5] 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 longer than 60 min led to increasingly severe toxicity including bone marrow suppression and liver enzyme elevation.

Pre-clinical data suggested that frequent dosing was required for optimal activity.[6] In addition, pharmacokinetic data suggested that plasma levels of gemcitabine of 20 μmol/l are needed for optimal accumulation of gemcitabine tri-phosphate in mononuclear cells. This level can be achieved by doses of 350 mg/m^2 and

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greater when a 30 min infusion of gemcitabine is used. The weekly and every other week schedule administered doses high enough to achieve this. However, since responses were seen using the weekly schedule and because it was well tolerated, the schedule administering gemcitabine every week for 3 weeks followed by a fourth week of rest (1 cycle) was chosen for the phase II studies. A dose of 800 mg/m^2 administered as a 30 min infusion was initially chosen. As weekly scheduling is not very practical and the day 15 treatment is often omitted when given in combination, especially with cisplatin, a day 1 and 8 every 21 days schedule is being explored.

Several phase II studies using gemcitabine have been completed and activity was observed in advanced pancreatic cancer,[7-10] epithelial ovarian cancer,[11-14] advanced breast cancer,[15-17] small cell lung cancer,[18] bladder cancer,[19-21] and head and neck cancer.[22] In non-small cell lung cancer (NSCLC), consistent response rates of around 20% and above have been recorded after verification by an independent Oncology Review Board.[23-26] These results are, however, promising, as NSCLC is notoriously difficult to treat and existing standard treatments give response rates of only 15–20% when used as single agents and are often associated with significant toxicity.[27]

To evaluate the safety profile of gemcitabine in detail, safety data from all completed clinical studies using the once weekly treatment regimen were combined. The integrated safety database consisted of 22 studies across a range of solid tumors and included 979 patients who had received at least one dose of gemcitabine. The WHO guidelines were used for assessment of toxicity and as the maximum grade experienced was recorded for each patient in these studies, they represent a rigorous criterion for assessment. However, certain adverse events occurred which are not addressed by the WHO system and these are described separately.

The analysis of laboratory toxicity included all 979 patients and grades were allocated by computer comparison to the normal range irrespective of causality (Tables 1 and 2). Non-laboratory toxicity parameters were assigned by the investigators and there were differences in practice between the investigators taking part in the original US coordinated studies and those taking part in studies coordinated from Europe. Investigators in the original US studies assigned WHO toxicity grades to all toxicities regardless of causality, whereas investigators in European studies only assigned toxicity grades when the event was considered possibly related to gemcitabine administration. Because of this difference, only the European database and more recent US studies, i.e. 565 patients, have been used for the examination of WHO non-laboratory parameter toxicities, as this was considered to best represent the toxicity of the drug (Table 3). Other safety parameters discussed include serious adverse events and treatment-emergent signs and symptoms (TESS). The latter are events irrespective of causality that occurred for the first time during active treatment or conditions present at baseline that

Table 1. WHO recommended toxicity gradings

Toxicity parameter	Maximum WHO grades (% of patients)				
	0	1	2	3	4
Hematological					
hemoglobin g/100 ml	≥11.0	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
g/l	≥110	95–109	80–94	65–79	<65
mmol/l	≥6.8	5.6–6.7	4.95–5.8	4.0–4.9	<4.0
leukocytes $\times 10^9$/l	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
granulocytes $\times 10^9$/l	≥2.0	1.5–1.9	1.0–1.4	0.5–0.9	<0.5
platelets $\times 10^9$/l	≥100	75–99	50–74	25–49	<25
Liver					
ALT/AST $\times$ N[a]	≤1.25	1.26–2.5	2.6–5	5.1–10	>10
alkaline phosphatase $\times$ N[a]	≤1.25	1.26–2.5	2.6–5	5.1–10	>10
bilirubin $\times$ N[a]	≤1.25	1.26–2.5	2.6–5	5.1–10	>10
Renal	≤1.25	1.26–2.5	2.6–5	5–10	>10
Blood urea nitrogen $\times$ N[a]		1+	2–3+	4+	
Proteinuria g%	no change	<0.3	0.3–1.0	>1.0	nephrotic syndrome
g/l		3	3–1.0	>10	obstructive uropathy
Hematuria	no change	microscopic	gross	gross and clots	

[a] Normal range of our laboratory.

Table 2. Summary of maximum WHO toxicity grades for laboratory data (patients receiving therapy=979)

Toxicity parameter	Maximum WHO grades (% of patients)				
	0	1	2	3	4
Hemoglobin	32.4	38.5	21.0	6.8	1.3
Leukocytes	37.7	24.4	28.5	8.6	0.7
Platelets	75.7	11.4	7.7	4.1	1.1
Segmented neutrophils[a]	36.8	16.6	21.2	19.3	6.0
Liver toxicity					
alkaline phosphatase (pretreatment value)	44.7 (67.6)	29.7 (20.6)	17.1 (9.1)	6.6 (2.1)	1.9 (0.6)
ALT (pretreatment value)	32.3 (87.1)	36.9 (10.6)	21.2 (2.0)	7.9 (0.3)	1.7 (0.0)
AST (pretreatment value)	32.8 (83.7)	39.3 (13.3)	19.5 (2.5)	6.5 (0.4)	2.0 (0.1)
bilirubin (pretreatment value)	87.4 (97.3)	7.1 (2.2)	2.8 (0.4)	1.8 (0.1)	0.8 (0.0)
Renal toxicity					
blood urea nitrogen	83.8	14.2	2.0	0.0	0.0
creatinine	92.5	7.0	0.4	0.1	0.0
hematuria[b]	69.3	27.6	2.9	0.2	0.0
proteinuria[c]	64.5	32.9	2.3	0.4	0.0

[a]Segmented neutrophils have been converted to WHO scores using granulocyte count criteria.
[b]No clinical information was available from Lilly case report forms and WHO grades could not be correctly allocated. All reported urinalysis values were converted to a grading scale as follows: dipstick result, g/l, grade: nil, –, 0; + or trace, <3 g/l, 1; ++ or +++, 3–10 g/l, 2; ++++, >10 g/l, 3. Allocation of grade 4 toxicity was not possible. Any report of hematuria greater than grade 0 can only be interpreted to indicate the presence of microscopic hematuria. This system overestimates the number of patients with WHO grade 2 and 3 hematuria.
[c]No clinical information available from Lilly case report forms and WHO grades were derived from urinalysis data. Therefore, allocation of grade 4 toxicity (nephrotic syndrome) was not possible.

worsened during treatment. Table 4 lists serious adverse events reported during gemcitabine studies for all 979 patients.

Hematological toxicity

Hemoglobin

WHO grade 3 and 4 hemoglobin toxicities were recorded in only 6.8 and 1.3% of patients, respectively, in the gemcitabine database (Table 2). A serious adverse event of anemia irrespective of causality was reported for 5.0% of patients but only 0.2% (two) of patients were discontinued for anemia. In most cases the anemia was only considered to be serious because of the policy of hospitalizing patients for transfusion. There was no evidence of cumulative toxicity and previous chemotherapy did not significantly influence the frequency or severity of anemia. In addition, only 0.1% of doses (14 out of 10 793) were adjusted for anemia, although the reasons for dose adjustments were unspecified for 4% of doses.

Table 3. Summary of maximum WHO toxicity grades for non-laboratory data (European database, patients receiving therapy=561)

Toxicity parameter	Maximum WHO grades (% of patients)				
	0	1	2	3	4
Allergic	96.6	2.9	0.4	0.2	0.0
Constipation	92.2	5.5	1.6	0.7	0.0
Cutaneous	75.2	15.5	9.1	0.2	0.0
Diarrhea	87.9	8.2	3.2	0.7	0.0
Fever	62.7	20.9	15.7	0.7	0.0
Cardiac function	98.6	0.7	0.0	0.5	0.2
Hair	85.9	10.3	3.4	0.4	0.0
Hemorrhage	97.9	1.0	0.7	0.0	0.3
Infection	91.3	5.9	1.6	1.1	0.2
Nausea/vomiting	35.7	26.6	19.4	17.1	1.2
Oral	91.6	5.9	2.3	0.2	0.0
Pericarditis	99.8	0.2	0.0	0.0	0.0
Peripheral neurotoxicity	96.8	2.9	0.4	0.0	0.0
Pulmonary	92.3	4.5	1.8	1.2	0.2
Cardiac rhythm	97.9	1.4	0.5	0.2	0.0
State of consciousness	90.9	4.5	3.7	0.9	0.0

Leukocytes and neutrophils

WHO grade 3 and 4 leukocyte toxicity was seen in 8.6 and 0.7% of patients, respectively, and the corresponding figures for neutrophil toxicity were 19.3 and 6.0% (Table 2). Leukopenia was reported as a serious event in 0.6% (six out of 979) of patients and resulted in only one patient (0.1%) discontinuing from the study. There

Table 4. Summary of serious adverse events according to Good Clinical Practice definition reported during gemcitabine studies

Event classification	All [*n*=979 (%)]
Gastrointestinal	
nausea	4.5
vomiting	5.1
abdominal pain	2.3
constipation	0.9
ileus	0.7
Skin/hair	
cellulitis	0.7
Infection/fever	
fever	5.2
pneumonia	1.3
Cardiovascular	
chest pain	0.8
deep thrombophlebitis	1.5
peripheral edema	1.7
Pulmonary	
hemoptysis	0.6
dyspnea	4.9
Pain	2.2
Fluid imbalance	
ascites	1.4
pleural effusion	1.5
dehydration	2.2
Hematological	
anemia	5.0
thrombocytopenia	1.2
Cancer	
carcinoma of the lung	1.1
carcinoma	0.5
Other	
accidental overdose	0.7
chills	1.3
asthenia	1.9

was no evidence of cumulative toxicity but previous chemotherapy appeared to increase the frequency and severity of leukopenia for leukocytes; grade 3 and 4 toxicity was seen in 14.6% of pretreated patients compared with 8.0% of chemonaive patients. For neutrophils, grade 3 and 4 toxicity occurred in 30.5 and 24.1% of pretreated and chemonaive patients, respectively. In both groups, this toxicity was rarely dose limiting. Overall, 4.3% (461 out of 10 793) of doses overall were adjusted for leukopenia, although the reasons for dose adjustments were unspecified for 4% of doses. Many of these dose adjustments were protocol driven since in the early studies the protocol requirements for dose adjustments were somewhat conservative, i.e. a WBC count of $2\text{-}2.9 \times 10^9$/l required a 50% dose reduction and a WBC of less than 2×10^9/l mandated a dose omission. The lack of clinical significance of this neutropenia was reflected by the low incidence of infection, with WHO grade 3 toxicity for infection (major infection) being reported in only 1.1% (six out of 979) of patients and no grade 4 toxicity reported.

Platelets

Thrombocytopenia was not a significant problem and was rarely dose limiting (Table 2). Thrombocytopenia was reported as a serious adverse event in 1.2% of patients (12 out of 979); only 0.7% of patients (seven out of 979) received platelet transfusions and only 0.4% of patients (four out of 979) discontinued treatment because of thrombocytopenia. No signs of cumulative platelet toxicity were noted. Patients previously treated with cytotoxic chemotherapy tended to show more pronounced platelet toxicity as grade 3 and 4 toxicity occurred in 8.8 and 4.4% of patients in the pretreated and chemonaive patient groups, respectively. Serious adverse events reported for hemorrhage were in most cases disease-related.

Thrombocytopenia is an expected toxicity of cytotoxic treatment. However, 6.2% of patients (61 out of 979) reported thrombocythemia. This event may have been under-reported as it was not thought to have clinical importance. It probably related to a rebound phenomenon following administration of this myelosuppressive agent. However, the lack of clinical importance is supported by the fact that none of these cases were considered serious and no patient discontinued treatment because of thrombocythemia. In addition, below 0.1% (two out of 10793) of doses were adjusted for thrombocythemia.

Gastrointestinal toxicity

Liver toxicity

The liver is responsible for the metabolism of many drugs, and thus is vulnerable to any toxic effects of these drugs and their metabolites. In particular, hepatotoxicity has been observed during treatment with etoposide, cytosine arabinoside and methotrexate.

At entry into the gemcitabine studies, two-thirds of the patients in this dataset had at least one abnormal liver function test at baseline and one-third had documented liver metastases. More specifically, at study entry WHO grades 1 or above were recorded for 2.7% (26 out of 960) patients for bilirubin, 32.4% (311 out of 960) for alkaline phosphatase, 12.9% (97 out of

752) for alanine transaminase (ALT) and 16.3% (150 out of 918) for aspartate transaminase (AST). During the studies, liver enzymes remained normal in approximately one-third of patients (Table 2). The toxicity was manifest as a transient, asymptomatic, rapidly reversible elevation of the enzymes. WHO grade 3 or 4 toxicity occurred in 2.6, 9.6, 8.5 and 8.5% of patients for bilirubin, ALT, AST and alkaline phosphatase toxicities, respectively. Gemcitabine does, however, appear to induce a mild transaminitis in a significant number of patients as is reflected by the fact that 41.7% (1126 out of 2703) of cycles with data had grade 1 or 2 toxicity for ALT and 43.6% (1406 out of 3225) of cycles had grade 1 or 2 toxicity for AST. These increases were rarely of clinical significance as was demonstrated by only 0.5% (five out of 979) of patients being withdrawn and only 0.5% (58 out of 10 793) of protocol-defined injections being adjusted for hepatotoxicity. In addition, there was no evidence of cumulative hepatotoxicity.

Constipation

Constipation (generally mild) was reported in 7.8% of patients (Table 3). The majority of these reports were for mild constipation (WHO grade 1). There were four reports of grade 3 toxicity, defined as abdominal distention, but no reports of grade 4 toxicity. There were 0.9% reports of serious constipation, but no patients were discontinued and no doses were adjusted for this reason, although 4% of doses were adjusted for unspecified reasons. Moreover, the assessment of drug causality may have been complicated by the concomitant use of morphine-like analgesics and serotinin receptor antagonists in a large number of patients.

Nausea and vomiting

For patients, nausea and vomiting is the most distressing side effect of chemotherapy. Some will experience nausea and vomiting just with the anticipation of treatment. The timing of onset varies from drug to drug and in some cases symptoms may persist for up to 2 weeks. Fortunately, prophylactic antiemetics may abolish vomiting and reduce nausea.

WHO grade 3 and 4 toxicity for nausea and vomiting was recorded in 17.1 and 1.2% of gemcitabine-treated patients, respectively (Table 3). It should be noted that the WHO gradings, especially grade 3 nausea and vomiting, are highly dependent upon the local policy for treating nausea and vomiting, and the acceptability of nausea and vomiting by the patients. Some investigators gave prophylaxis for emesis to all patients, other investigators did not give prophylaxis to any patients and prophylactic antiemetics varied from low-dose metoclopramide to high-dose ondansetron in a few cases. In addition, the extensive use of morphine-like analgesics may have complicated the assessment of drug causality and therefore biased the allocation of WHO grades.

Nausea and vomiting were rarely dose-limiting, only 0.2% (22 out of 10 793) of doses were adjusted for nausea and/or vomiting although 4% of doses were adjusted for unspecified reasons. In addition, only 0.2% (two out of 979) of patients were discontinued for this reason.

Diarrhea

There was no grade 4 toxicity and only four patients (0.7%) reported grade 3 toxicity (Table 3). No patient withdrew because of diarrhea, only one patient reported diarrhea as a serious adverse event and below 0.1% (10 out of 10 793) of doses were adjusted for diarrhea, although 4% of doses were adjusted for unspecified reasons.

Oral toxicity

Mucositis may be a significant problem following administration of chemotherapy and when serious may result in patients being unable to take food by mouth. However, oral toxicity was not an important clinical problem. It was reported by 8.4% of patients (Table 3) but was predominantly mild with 5.9% of patients having grade 1 toxicity (soreness or erythema). No grade 4 toxicity was reported. Only one patient reported grade 3 toxicity (ulcers requiring a liquid diet) and was the only patient to withdraw because of oral toxicity.

Urinary tract toxicity

Of patients in this dataset, 17.9% had either renal or prostate cancer in which abnormalities in renal function or urinalysis might not be drug related or ovarian cancer which would have been previously treated with prior nephrotoxic platinum-containing regimens. No WHO grade 4 toxicity was seen for BUN or creatinine during treatment with gemcitabine (Table 2). There was one report of grade 3 toxicity

for creatinine (0.1%) but none for BUN. There was no suggestion of cumulative toxicity.

Proteinuria was frequently reported, but was mild in the majority of cases. WHO toxicity grades for proteinuria were derived from the investigators' assessment of the WHO grade. Grade 3 proteinuria toxicity ('4+' on urine dipstick or greater than 10 g/l) was seen in 0.4% of patients. WHO grade 2 toxicity ('2+' or '3+', or 3–10 g/l) occurred in 2.3% of patients. WHO grade 1 toxicity ('1+' or below 3 g/l) occurred in 32.9% of patients. The incidence of low grade proteinuria might reflect the sensitivity and specificity of the urine sample dipstick as well as the possible toxicity of the drug. One patient was discontinued due to albuminuria and below 0.1% (three out of 10793) of protocol-defined injections were adjusted for albuminuria, although 4% of doses were adjusted for unspecified reasons.

Hematuria was assessed by different methods, including both conventional 'urine dipstick' as well as formal laboratory microscopy, and the grading was assigned by the investigators. There were no reports of hematuria for 69.3% of patients. Grade 1 hematuria was reported in 27.6% of patients, grade 2 in 2.9% of patients and grade 3 in 0.2% of patients.

In the two pancreas studies[9,10] where the WHO grades were strictly interpreted, only 8.7% of patients had grade 1 hematuria and no toxicity greater than grade 1 was seen.

One patient was discontinued due to hematuria and below 0.1% (six out of 10793) of protocol-defined injections were adjusted for hematuria, although 4% of doses were adjusted for unspecified reasons.

Nephrotoxicity caused discontinuation of therapy in 0.5% (five out of 979) of patients. Hemolytic uremic syndrome was documented or suspected in four of these cases, although one of the cases had received prior mitomycin therapy. Mitomycin has been frequently reported to cause microangiographic hemolytic anemia with renal failure in some patients.[28] In addition, two other patients developed acute renal failure after discontinuing from the study and both these cases had a clinical picture compatible with hemolytic uremic syndrome. Two of the cases had either renal biopsy or autopsy findings compatible with the diagnosis of hemolytic uremic syndrome. It is reasonable to expect this incidence of hemolytic uremic syndrome (0.6%) in a group of advanced cancer patients such as this. However, although these cases are rare, gemcitabine should be used with caution in patients with impaired or deteriorating renal function. Studies in patients with organ (renal or liver) dysfunction are almost completed (data on file; Eli Lilly).

Overall, although mild changes in renal laboratory parameters were frequently reported they were rarely clinically significant. A number of cases of renal failure of uncertain etiology have been reported during treatment with gemcitabine.[25]

Pulmonary and allergic toxicity

Of the patients used for the WHO toxicity analysis for pulmonary toxicity, 43% (243 out of 565) had NSCLS and 49.6% (280 out of 565) had either primary or metastatic disease in the lung at study entry. Therefore, this population probably had a significant amount of pulmonary dysfunction at study entry. Drug-related dyspnea was reported in 7.7% of patients (Table 3), but it was usually mild and rarely required specific therapy. Only one patient was discontinued due to drug-related dyspnea. Severe dyspnea occurred in some patients, with grade 3 toxicity being reported in 1.2% and grade 4 in one patient (Table 3). Analysis comparing lung cancer patients with non-lung cancer patients did not show a higher incidence of WHO grades for pulmonary toxicity in the lung cancer studies (7.7 versus 7.5%). Grade 3 or 4 pulmonary toxicity was reported in 1.4% (six out of 242) of the lung cancer patients and 0.6% (two out of 318) of the non-lung cancer patients.

The dyspnea generally occurred within a few hours of gemcitabine administration and usually lasted for a short time (1–6 h). It appeared that some patients developed dyspnea after administration of gemcitabine which was associated with bronchospasm. This led to an analysis of the WHO criteria for allergic toxicities; grade 2 for allergy is bronchospasm not requiring parenteral therapy, grade 3 is bronchospasm requiring parenteral therapy and grade 4 is anaphylaxis.

This analysis showed that 96.6% (542 out of 561) of patients had no allergic toxicity, 0.4% (two out of 561) had grade 2 and 0.2% (one out of 561) had grade 3 with no patients having grade 4 allergic toxicity recorded as their maximum toxicity. Obviously, a short-lived toxicity such as bronchospasm might be worse on a by-cycle analysis but this was not the case. In the database of 1982 cycles there were only 0.1% (two of 1982) of cycles associated with grade 2 and less than 0.1% (one out of 1982) with grade 3 and no grade 4 toxicity. Only 0.7% (seven out of 979) of patients were discontinued from the study because of dyspnea, bronchospasm or asthma. The dyspnea usually abated spontaneously without any specific therapy, although there

were anecdotal reports of improvements with steroids and bronchodilators.

With regard to other clinical sequelae of pulmonary toxicity, 1.3% (13 out of 979) of patients were withdrawn from the studies for 'any pulmonary event' (this includes the seven patients mentioned above). Only 0.6% (70 out of 10793) of protocol-defined injections were adjusted for pulmonary toxicity.

Less than 1% of patients developed dyspnea associated with a pulmonary infiltrate. It was not accompanied by an eosinophilia and was generally reversible on withdrawal of the drug, steroid therapy or both. Recently, however, acute respiratory distress syndrome has been reported in three patients following gemcitabine administration.[29] In two patients it was fatal.

Alopecia

Alopecia is a frequent side effect of chemotherapy and is a result of damage to hair follicles. The extent of alopecia increases with increased dose of drug. Generally, only the head hair is lost but the whole of the body hair may be affected. Of drugs commonly used in NSCLC, all patients receiving etoposide suffer from hair loss and 15% experience complete alopecia,[29] and complete hair loss is usually universal following chemotherapy which includes ifosfamide.[30] With paclitaxel, total alopecia occurs in nearly all patients.[31]

Overall, gemcitabine caused little hair toxicity and 85.9% of patients had no hair loss at all (Table 3). No grade 4 toxicity (non-reversible alopecia) was reported and only 0.4% of patients[3] reported grade 3 toxicity (complete but reversible alopecia). WHO grade 1 toxicity (minimal hair loss) was reported for 10.3% of patients and 3.4% of patients reported grade 2 toxicity (moderate, patchy alopecia).

Cutaneous toxicity

Cutaneous toxicity was reported for 24.8% of patients. However, this was predominantly mild. There was no grade 4 toxicity (defined as necrosis requiring surgery) and only one patient (0.2%) reported grade 3 toxicity (defined as moist desquamation and ulceration). The majority of the reported toxicities were mild (WHO grade 1: erythema) or moderate (WHO grade 2: dry desquamation, vesiculation or pruritus). Only 0.7% events of serious rash were reported, with 0.2% resulting in early discontinuation due to rash or urticaria and only 0.1% (16 out of 10793) of doses were adjusted for rash or urticaria, although 4% of doses were adjusted for unspecified reasons.

TESS were collected to assess events and thus help delineate toxicities not covered by the WHO toxicity grades. However, it should be noted that TESS are defined as any change in the clinical status of the patient regardless of causality. Therefore it includes any cancer-related changes. The most commonly reported relevant TESS events were rash (21.3%), maculopapular rash (3.5%) and vesiculobullous rash (1.0%). Pruritus was reported for 8.7% of patients. Moreover, very few adverse events (TESS) secondary to gemcitabine extravasation were reported. Of 979 patients, 'injection site pain' was reported in 1.4% of patients, 'injection site hemorrhage' in 0.3% of patients, 'injection site inflammation' in 0.4% of patients, 'injection site reaction' in 1.2% of patients, 'injection site edema' in 0.2% of patients and 'injection site hypersensitivity' in one patient. None of these adverse events were considered to be serious and there were no reports of 'injection site necrosis.'

Neurological toxicity

Severe neurological problems may be associated with anticancer drugs. Peripheral neuropathy is most commonly seen and is the major non-hematological dose-limiting effect with higher doses of paclitaxel.[31] It is also a problem with the vinca alkaloids and cisplatin.

Somnolence was reported in 9.1% of gemcitabine-treated patients. This was usually mild or moderate in severity with only 0.9% of patients reporting serious adverse events due to somnolence. Only one (one out of 10793) protocol-defined injection was adjusted for somnolence.

Asthenia was commonly reported (42%) as an event irrespective of causality. This was considered to be a toxicity by some investigators but the true incidence is confounded by the natural history of the primary disease. In 1.9% of patients asthenia was categorized as serious, but only 0.3% (28 out of 10793) of protocol-defined injections were adjusted for this reason.

WHO grade 1 or 2 peripheral neurotoxicity was reported in 3.3% of gemcitabine-treated patients. Grade 3 and 4 toxicity was not reported.

Cardiac toxicity

A number of cytotoxic drugs are potentially cardiotoxic, anthracyclines probably being the most well known for causing cardiomyopathy.[32] There is evidence that this cardiac damage is reduced by con-

comitant administration of dexrazoxane, but some patients may still develop congestive heart failure, years after treatment.[33] A wide range of generally asymptomatic and not usually serious cardiac disturbances have been reported during paclitaxel administration.[31] A number of serious cardiovascular effects have also been reported during infusion of paclitaxel and it should be administered with caution to patients with pre-existing cardiovascular disease, especially if combined with doxorubicin.[34]

During treatment with gemcitabine, there were a few serious incidences of myocardial infarction (0.5%), congestive heart failure (0.4%) and arrhythmia (0.2%) as would be expected in such a patient population. In some cases, the relationship of these cardiac events to gemcitabine could not be excluded and therefore they were assigned WHO toxicity grades. There was one report of grade 4 cardiac function toxicity, defined as symptomatic dysfunction not responsive to therapy. There were also three reports of grade 3 cardiac function toxicity (symptomatic dysfunction responsive to therapy). A few cases of hypotension were also reported. One patient reported grade 3 cardiac rhythm toxicity (multifocal premature ventricular contractions) but no patient reported WHO grade 4 cardiac rhythm toxicity (ventricular tachycardia). The only report of a WHO grade for pericarditis was one patient who had a grade 1 toxicity (asymptomatic effusion).

Overall, 1.7% of patients were discontinued due to cardiovascular events. Four patients were discontinued following a myocardial infarction, two patients each due to the following events: arrythmia, chest pain, heart failure, pulmonary edema and hypertension; and one due to each of the following: abnormal electrocardiogram, deep thrombophlebitis and hypotension. Only 0.3% (28 out of 10793) of protocol-defined doses were adjusted for any cardiovascular event, although 4% of doses were adjusted for unspecified reasons.

Adverse events not covered by WHO toxicity gradings

Certain events are not covered by WHO grading system and were recorded separately for all 979 patients.

Flu-like symptoms and fever

A number of patients reported flu-like symptoms, which commonly included headache, back pain, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise and insomnia were also reported. These events were reported separately with frequencies approaching 45%. It was not possible to estimate how many cases were due to actual viral infection.

Data collection for this event differed between centers. Some investigators reported the flu-like symptoms as a discrete entry, whereas others reported individual symptoms, e.g. myalgia, fever, chills, etc. Flu-like symptoms were reported in 18.9% of the 979 patients. Flu-like symptoms were generally mild. There were 0.9% of patients who had serious flu-like symptoms, but only one patient discontinued early due to this event.

In addition, less than 0.1% (seven out of 10793) of protocol-defined injections were adjusted for the flu-like symptoms, although 4% of doses were adjusted for unspecified reasons.

Overall, flu-like symptoms commonly reported were usually mild, of short duration and rarely dose limiting. The mechanism of this event is unknown, although some patients were reported to have had alleviation of symptoms with paracetamol.

It was not possible to estimate the percentage of patients with flu-like symptoms associated with fever. However, by TESS which includes disease-related symptoms, fever was reported much more frequently (44.2%) than flu-like symptoms (18.9%), thus indicating that fever was reported in the absence of the flu-like symptoms.

The WHO grades for fever were analyzed and 62.7% (352 out of 561) of patients with data had no fever. The fever was generally mild, with 205 of the 209 patients reporting fever having grade 1 or 2 (below 40°C). Only three patients were discontinued for fever; 5.2% of patients reported fever as a serious adverse event regardless of cause. Of these 51 serious cases of fever, only six occurred in the setting of severe neutropenia. The incidence of fever contrasts with the incidence of patients reporting infection and indicates that gemcitabine may cause fever in the absence of clinical infection; 37.3% of patients reported WHO grade 1 or greater toxicity for fever, whereas WHO grade 1 or greater toxicity for infection was reported for only 8.7% of patients. There was one report (0.2%) of grade 4 infection toxicity (major infection with hypotension) and six reports (1.1%) of grade 3 infection toxicity (major infection). Moderate infection (WHO grade 2) was reported for 1.6% of patients and minor infection (WHO grade 1) was reported for 5.9% of patients.

Edema

The term 'edema' was used to report different sites of subcutaneous edema, including peripheral edema, but was not used to report pulmonary edema which was reported in 1% of patients. The same event for a particular patient was sometimes reported under different categories at different visits. The events of edema, peripheral edema and face edema were reported (TESS) for 13.3, 20.3 and 0.9% of patients, respectively. In six out of 979 patients (0.6%) treatment was discontinued due to edema and in all cases was considered by the investigator to be drug-related. Overall, edema was frequently reported (up to 35% of patients) but was usually mild to moderate, reversible after stopping gemcitabine treatment and rarely resulted in discontinuation. The mechanism of this toxicity is unknown but it was not associated with any evidence of cardiac, hepatic or renal failure.

Other commonly reported adverse events

A number of other adverse events were commonly reported, e.g. weight loss, depression and anxiety. It was not possible to ascertain if these events were related to underlying malignancy or to gemcitabine treatment. Some events were clearly related to a particular site of disease or to a particular tumor type (e.g. hemoptysis, ascites and pleural effusion), and there was no evidence of a relationship between these events and gemcitabine.

Conclusions

The safety profile of single-agent gemcitabine was similar across all 22 phase II studies. As expected, a number of adverse events frequently associated with anticancer chemotherapy were encountered during gemcitabine treatment; these included myelosuppression and changes in gastrointestinal function. However, these occurred less frequently and were less severe than with many established drugs. Toxicities of great importance to the patient such as alopecia and mucositis were infrequent and mild. Some events less commonly seen with other anticancer chemotherapy were reported with gemcitabine administration, and included flu-like symptoms and edema unrelated to cardiac, hepatic or renal problems. Generally these were mild and rarely dose limiting.

Adverse events rather than reactions are reported in this paper as is appropriate under the Good Clinical Practice guidelines. Thrombocytopenia was the dose-limiting toxicity in many of the phase I studies probably because of heavy pretreatment status. It was less of a problem in the phase II studies with only 5.3% of patients having grade 3 or 4 toxicity. There were few associated problems with hemorrhage and infusions of platelets were rarely required. Leukopenia and neutropenia were more commonly reported but were usually short lived and rarely associated with infection. Myelosuppression typically did not require hospitalization or treatment with colony stimulating factors. This contrasts markedly with many of the other anticancer drugs used in the treatment of NSCLC. With ifosfamide 1.2 g/m^2/day, leukopenia was reported in 50% of patients and thrombocytopenia in 20%.[35] The severity increases with increasing dose. With single-agent paclitaxel, grade 4 leukopenia, granulocytopenia or neutropenia were reported in up to 100% of patients in clinical trials, although this figure has been reduced by the use of shorter infusion times and granulocyte colony stimulating factor.[31] Thrombocytopenia and anemia are less common. Myelosuppression is also dose-limiting for etoposide[29,36] and mitomycin C[37]. With etoposide, leukopenia (WBC $<3000/mm^3$ and WBC $<1000/mm^3$) occurs in 40 and 8% of patients, respectively. Anemia (Hb <11 g/dl) occurs in around 42% of patients and thrombocytopenia (platelets $<100\,000/mm^3$) in around 14% of patients. With mitomycin C, leukopenia (WBC $<4000/mm^3$) occurs in up to 71% of patients and thrombocytopenia (platelets $<100\,000/mm^3$) in up to 90% of patients, depending on schedule. In contrast, hematological toxicity was not found to be a significant problem during gemcitabine treatment.

Mild changes in renal toxicity parameters, particularly urinalysis, occurred frequently but were rarely of clinical significance. However, some cases of renal failure of uncertain etiology were recorded. It is recommended that gemcitabine is used with caution in any patients developing signs of renal dysfunction and is discontinued at the first signs of any evidence of hemolytic uremic syndrome. Once again this mild renal toxicity profile contrasts marked with those of the standard therapies. Renal toxicity is commonly reported with cisplatin. Symptoms vary from an asymptomatic rise in serum creatinine or mild proteinuria, to acute renal failure with anuria requiring dialysis. In early clinical studies of cisplatin, nephrotoxicity was the major dose-limiting toxicity in 30–50% of patients[38,39] and with ifosfamide, severe cystitis was observed in 20–40% of patients.[35,40] The renal damage caused by cisplatin may be minimized by ensuring the patient is adequately hydrated before, during and after treatment but, even so, a subclinical reduction in kidney function occurs. Ifosfamide may cause chemi-

cal cystitis due to the presence of its acrolein metabolite in the urine. With ifosfamide, administration of the sulfhydryl group donator mercaptoethane sulfonic acid (mesna) ensures neutralization of acrolein which helps prevent renal damage.[35,39]

Gemcitabine is associated with frequent transient rises in transaminases, but again, these are rarely of clinical significance.

Events such as anemia are serious because they result in the patient being hospitalized and thus fulfilling the definition of serious. Usually the patient was hospitalized because of local policies to admit patients for transfusions. In addition fever, when reported as an event regardless of toxicity, was reported in 44% of patients but in only 37% was it rated as a toxicity. Thus demonstrating that events include disease-related phenomena.

Gemcitabine was well tolerated as is shown by the fact that in this database of 979 patients, 3521 cycles and 10 120 administered injections, 25% of doses were escalated, and only 6% were omitted and 14% reduced, despite somewhat conservative protocol requirements for dose adjustment. Overall, 94% of protocol-defined injections were actually given. The good tolerance is further confirmed by looking at the WHO grade 3 and 4 toxicities for non-laboratory parameters. Of the 16 WHO-defined parameters which were assessed, the only parameters which show an incidence of 1% or greater are infection (1.2%), nausea and vomiting (18.4%), and pulmonary toxicity (1.4%).

In conclusion, gemcitabine has a mild toxicity profile which makes it an attractive cytotoxic drug. The short-lived myelosuppression and non-overlapping toxicity profile makes gemcitabine an ideal candidate for trial in combination with other cytotoxic agents.

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