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Phase II trials of single-agent activity of gemcitabine in patients with advanced non-small cell lung cancer: an overview

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A total of 361 patients have been entered into four phase II trials in which gemcitabine was given as a 30 min infusion in a schedule weekly × 3 q4W, at starting doses of 800–1250 mg/m^2. Three of these trials produced response rates of 22.5%, 20% and 21.8% (all response rates were independently evaluated by an extramural Oncology Review Board). One small study of 30 evaluable patients produced a disappointing low response rate of 3%, but in this study the mean and median dose delivered was under 700 mg/m^2. Gemcitabine was well tolerated with modest levels of traditional cytotoxicities such as myelosuppression, nausea and vomiting, and alopecia. Pooled data from two of the studies show improvement in a number of disease-related symptoms. Objective response rates by prognostic factor were determined: stage IIIa (30.5%), stage IIIb (18.8%), stage IV (19.5%); performance status 0 (31.8%), 1 (16.7%) and 2 (21.7%); female gender (23.5%), male (17.5%); age < 70 (18.6%), age > 70 (21.9%). Gemcitabine can be considered for use as a single agent in patients unable or unwilling to tolerate combination chemotherapy. Dose–response data suggest that a dose of 1000 mg/m^2 or more is required for optimal therapeutic effect. The single-agent activity of gemcitabine together with its non-overlapping toxicity and novel mode of action suggest that this agent should also be investigated in combination with other active agents in non-small cell lung cancer.

Introduction

Gemcitabine (2',2'-difluorodeoxycytidine) is a new nucleoside analogue which is structurally similar to the antimetabolite cytosine arabinoside (ara-C). Despite this structural similarity gemcitabine's cellular pharmacology and mechanism of action differ markedly,[1] and in preclinical testing it was shown to have significantly greater activity in a wide variety of solid tumour models.[2] Both gemcitabine and ara-C are phosphorylated by the enzyme deoxycytidine kinase into their active triphosphate metabolites. However, the intracellular concentration of gemcitabine triphosphate is 20-fold greater than that seen for ara-C triphosphate at equimolar concentrations of the parent drugs. This may be due either to increased membrane permeability for gemcitabine or increased affinity for the deoxycytidine kinase enzyme. Furthermore, these high intracellular levels of the active compound are prolonged through an interesting process of self-potentiation since the diphosphate facilitates increased gemcitabine phosphorylation and the active triphosphate inhibits the deaminase which is necessary for the breakdown and metabolism of gemcitabine. Thus, gemcitabine's increased activity against solid tumours may be the result not only of higher cumulative intracellular levels of the active metabolite, but also of the more prolonged duraton of activity before it is broken down to inactive forms. The active triphosphate forms a substrate for incorporation into the elongating DNA chain. After the incorporation of the gemcitabine nucleotide, one more nucleotide is allowed to pair before chain elongation is terminated, so-called "masked DNA chain termination". In this way the gemcitabine nucleotide is not in the terminal position and is less susceptible to detection and repair by "proof-reading" exonucleotide action.

These intriguing preclinical observations led to the initiation of several phase I studies of gemcitabine to determine the most appropriate dose and schedule of administration for this interesting new agent. There were *in vitro* data to suggest that the anti-tumour activity of gemcitabine was schedule dependent,[2] and in phase I clinical testing the toxi-

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city profile for the drug also varied greatly according to the schedule of administration. The phase I dose-finding and toxicity trials have been reviewed recently by Fossella.[3] When given daily for 5 days in a schedule similar to that of ara-C, the maximum tolerated dose was only 12 mg/m^2/day every 3 weeks, and at this level most patients experienced unacceptable flu-like symptoms, and severe or even life-threatening episodes of hypotension were encountered. When given twice a week for 3 weeks with a 1 week break, higher doses of gemcitabine could be administered and the toxicity profile changed. Life-threatening hypotension was no longer seen, although a small percentage of patients continued to have flu-like symptoms. The dose-limiting toxicity on this schedule was thrombocytopenia and the maximum tolerated dose was 65 mg/m^2/infusion when the drug was given over 30 min and 150 mg/m^2/infusion when it was given as a 5 min bolus. By increasing the interval between treatments and administering gemcitabine every second week, doses of 3,000 to > 4,000 mg/m^2 every 2 weeks could be administered safely. Dose-limiting toxicity with this schedule was bone marrow suppression with anaemia, neutropenia and thrombocytopenia.

The schedule which combined activity with the most favourable toxicity profile was gemcitabine administered once weekly for 3 weeks with a 1 week rest.[3] With this schedule myelosuppression and in particular thrombocytopenia was the dose-limiting toxicity, and in previously treated patients the maximum tolerated dose was 800 mg/m^2/week × 3 administered every 4 weeks. Other toxicities seen at this dose level included flu-like symptoms, transient skin rash, transient elevations of the hepatic enzymes and mild proteinuria and microscopic haematuria. These toxicities were not usually dose limiting. Significant hair loss and nausea and vomiting were not observed.

In these early phase I studies responses to gemcitabine were observed in patients with non-small cell lung cancer (NSCLC) and this led to several phase II trials of single-agent gemcitabine in *untreated* patients with NSCLC.[4] Gemcitabine weekly × 3 with a 1 week break was the schedule chosen for most of these trials, and the first studies were opened at a starting dose of 800 mg/m^2/week.

Early trials

Three studies, in North America, Europe and South Africa, were designed to evaluate gemcitabine's activity against advanced NSCLC using the weekly × 3 schedule. In these phase II trials, response rates were independently validated by an extramural Oncology Review Board. This board evaluated investigator-determined responders by reviewing the clinical history, signs, symptoms and appropriate radiological tests. The results of these trials are summarized in Tables 1, 2 and 3.

The first study was initiated in the US with a starting dose of gemcitabine 800 mg/m^2/week × 3.[4] Only 34 patients entered this trial, and many of these patients had received prior radiation. Twenty-six of the 34 had locally advanced Stage IIIa or IIIb tumours, and this was the only study that limited entry to patients of performance status 0 or 1. Despite these two favourable prognostic factors, a disappointingly low response rate of only 3% was seen in the 30 evaluable patients. However, the dose of gemcitabine delivered in this trial was low, both the mean and median doses being under 700 mg/m^2.

At the same time, a similar study was initiated in Manchester, England and Copenhagen, Denmark.[5] This trial also opened at a starting dose of gemcitabine 800 mg/m^2/week × 3. An analysis of toxicity seen in the American study and in the first cohort of patients in this European study demonstrated that toxicity was extremely mild, and that this dose was causing almost no myelosuppression. Therefore, for the second half of the European trial, the starting dose for gemcitabine was increased to 1,000 mg/m^2/week.

Eighty-two patients entered the trial, of whom 71 were evaluable for response. Sixteen partial responses were observed for an overall response rate of 22.5% (confidence interval: 13.5%–34%). The median duration of response was 8.1 months with a range of 3.6–17.3 months and the overall median survival was 8.1 months.

The third study was initiated in South Africa.[6] On the basis of toxicity data from the US and European studies, the starting dose of gemcitabine was 1,000 mg/m^2/week × 3. An analysis of toxicity from the second cohort of patients in the European study and the first cohort of patients in this South African study showed that, even with this elevated dose of gemcitabine, significant neutropenia and thrombocytopenia were not occurring. For that reason the starting dose in the South African study was increased to 1,250 mg/m^2/week × 3.

A total of 84 patients entered the study and 76 were evaluable for response. Two complete and 13 partial responses were observed for an overall response rate of 20% (confidence interval: 11.5%–30.5%). The median duration of response was 12.7

Table 1. Characteristics of patients in phase II trials of single-agent gemcitabine for non-small cell lung cancer

	American (n = 34)	European (n = 82)	South African (n = 84)	International (n = 161)
Gemcitabine starting dose (mg/m^2/wk × 3)	800	800–1000	1000–1250	1250
Male/female	28/6	49/33	65/19	124/37
Median age (range)	64 (40–78)	57 (23–71)	59 (36–75)	59 (35–75)
Median no. cycles (range)	2 (0–13)	4 (0–16)	3 (0–9)	3 (0–10)
Performance status	0, 1	0, 1, 2	0, 1, 2	0, 1, 2
Cell type				
Adenocarcinoma	18	53	22	70
Squamous	13	24	40	84
Other	3	5	22	7
Stage				
IIIa	} 26	18	15	7
IIIb		24	34	50
IV	8	40	35	104

Table 2. Response rates in phase II trials of single-agent gemcitabine for non-small cell lung cancer

	American (n = 34)	European (n = 82)	South African (n = 84)	International (n = 161)
Entered/Evaluable	34/30	82/71	84/76	161/151
Response				
CR	0	0	2 (3%)	3 (2%)
PR	1	16 (22.5%)	13 (17%)	30 (20%)
Overall response rate	3%	22.5%	20%	21.8%
95% CI	1%–17%	13.5%–34%	11.6%–30.5%	15.5%–29.3%
Response duration (months)				
Median	16.9	8.1	12.7	7.6
Range	N/A	3.6–17.3+	4.6–14.8+	2.6–19.6+
Median survival (months)	8.8	8.1	9.2	10.4

Table 3. Toxicity profile (WHO grades 3 and 4) in phase II trials of single-agent gemcitabine for non-small cell lung cancer

	European (n = 82)		South African (n = 84)		International (n = 161)	
	WHO 3	WHO 4	WHO 3	WHO 4	WHO 3	WHO 4
Anaemia	4.9	0	7.2	0	4.4	0.6
Leukopenia	6.2	1.2	9.6	1.2	7.0	0
Neutropenia	17.5	5.0	25.3	3.6	19.6	5.7
Thrombocytopenia	0	1.2	0	2.4	1.3	0
AST	3.3	1.6	3.6	0	6.3	2.5
ALT	10.0	7.5	4.8	2.4	10.8	1.9
Alkaline phosphatase	3.7	0	1.2	0	1.9	0
Bilirubin	0	0	0	0	0.6	0.6

months with a range of 4.6–14.8 months, and the median survival was 9.2 months.

As can be seen from Table 3, even in the studies which used the highest dose of gemcitabine, grade 4 neutropenia and thrombocytopenia were rarely encountered. Transient elevations of the hepatic enzymes were reported in all trials, but hepatic toxicity was rarely dose limiting. Other toxicities included mild flu-like symptoms, skin rash, mild fever on the day of treatment, proteinuria and microscopic haematuria, and lethargy. Visible hair loss was almost never encountered, and gemcitabine caused only mild nausea and vomiting which was usually prevented by the use of modest antiemetic agents.

Gemcitabine has also been evaluated in patients with NSCLC using other dosages and dose schedules. In a second trial performed in Manchester and Copenhagen, patients were treated with gemcitabine 90 mg/m^2 twice weekly.[7] The response rate of 19% was similar to that seen in the trials discussed above, but considerably more toxicity was encountered. Two-thirds of patients complained of severe flu-like symptoms and peripheral oedema, and one-quarter had grade 3/4 thrombocytopenia. In view of the poor therapeutic index, this schedule is not recommended. Finally, the same investigators are evaluating a 24 h infusion of gemcitabine once weekly for 3 weeks for patients with NSCLC.[8] The results of this study are still preliminary, but dose-limiting toxicity has not been seen at a dose of 180 mg/m^2/week.

Confirmatory trial

In an attempt to confirm the activity of gemcitabine seen in two of the first three phase II NSCLC trials discussed above, a large multicentre trial in advanced NSCLC was undertaken in Europe and Canada. Patients were eligible to enter this study if they had received no prior chemotherapy, although they could have received radiation therapy provided the evaluable lesions were not in the radiation treatment field. Patients with large cell anaplastic carcinoma were excluded since there had been a suggestion from the earlier trials that tumours of this cell type might be less responsive to gemcitabine. Patients were also excluded if they had a history of > 10% weight loss in the preceding 3 months. The starting dose for gemcitabine was 1,250 mg/m^2/week, and in this study dose escalation was permitted if grade 3 or 4 toxicity was not encountered in the previous cycle.[9]

The results of this trial are also included in Tables 1, 2 and 3. A total of 161 patients entered the study, of which 151 were evaluable for response. The median age was 59 years with a range of 35–75 years. The proportion of patients with adenocarcinoma and squamous cell carcinoma was approximately equal, and two-thirds of the patients had widely disseminated stage IV tumours. Three complete and 30 partial responses were seen for an overall response rate of 21.8% (confidence interval: 15.5%–29.3%). The median duration of response was 7.6 months with a range of 2.6–10.6 months. The median survival was 8.9 months.

Toxicity was mild. Grade 4 neutropenia was seen in only 5% of patients, and grade 4 thrombocytopenia was not encountered. The profile of non-haematologic toxicity was similar to that seen in the earlier three trials, and these toxicities were never dose limiting. Although some patients required dose reductions for toxicity, 25% of patients were able to tolerate increased doses, and in fact the actual dose delivered in this trial was 1,247 mg/m^2/week, close to the scheduled starting dose of 1,250 mg/m^2/week.

Symptom relief

Previous investigators have shown that it may not be necessary to achieve complete or even partial response to experience an improvement in tumour-related symptoms.[10] Improvement in specific symptoms was evaluated by Anderson and colleagues, using data pooled from the European and International gemcitabine studies.[11] Improvements, which had to be maintained for at least 4 weeks, were seen in the following symptoms: cough (44%), haemoptysis (63%), chest pain (32%), dyspnoea (26%) and anorexia (29%). Symptom improvement was even more marked in patients whose symptoms were classified as being either moderate or severe before starting treatment. One hundred per cent of patients had improvement in their haemoptysis; cough was improved in 73% and dyspnoea in 51%. The improvements in chest pain (37%) and anorexia (38%) were similar to those seen in patients who had only mild symptoms prior to treatment.

Prognostic factors

Several prognostic factors have been identified which may have a significant impact on response to chemotherapy and overall survival in patients with

Table 4. Response rate according to disease stage *

Stage at baseline	No. patients	Response	No response
IIIa	36	11 (30.5%)	25 (69.4%)
IIIb	101	19 (18.8%)	82 (81.2%)
IV	163	32 (19.6%)	131 (80.4%)
Total	300	62 (20.7%)	238 (79.3%)

* American, South African and International studies.

Table 5. Response rate according to pretreatment performance status *

Performance status at baseline	No. patients	Response	No response
PS 0	44	14 (31.8%)	30 (68.2%)
PS 1	264	44 (16.7%)	220 (83.3%)
PS 2	23	5 (21.7%)	18 (78.3%)
Total	331	63 (19.0%)	268 (81.0%)

* American, South African and International studies.

Table 6. Response rate according to patient gender *

Gender	No. patients	Response	No response
Female	85	20 (23.5%)	65 (76.5%)
Male	246	43 (17.5%)	203 (82.5%)
Total	331	63 (19.0%)	268 (81.0%)

* American, European, South African and International studies.

advanced NSCLC. In a large meta-analysis undertaken recently by Maki and Feld,[12] the most important prognostic factors included extent of disease (stage) and performance status. In some but not all trials, patients of female gender appear to have improved survival. Analyses of response according to various prognostic factors in the four single-agent trials discussed above are shown in Tables 4–8. With respect to stage, patients with stage IIIa tumours had the best overall response rate of 30.5%. Somewhat surprisingly, patients with stage IIIb tumours did not fare any better than those with stage IV tumours (response rates of 18.8% and 19.6% respectively). With respect to pre-study performance status, the results from the gemcitabine trials were similar to those reported by Maki and Feld.[12] An overall response rate of 31.8% was seen in patients with performance status 0 compared to 16.7% and 21.7% for those with performance status 1 and 2 respectively.

The results with respect to gender are also interesting. Female patients had an overall response rate of 23.5% compared to only 17.5% for males. These results may simply reflect the overall favourable prognosis associated with female gender, but they may also possibly reflect different metabolic patterns for gemcitabine in men and women. The clearance of gemcitabine from plasma in females is significantly slower than that seen in males.[13] Whether this may account for the improved response rate seen in females remains only speculative at this time.

No significant difference in response was seen in patients under 70 or over 70 years of age. If anything, the overall response rate of 21.9% in the small cohort of patients over 70 was slightly better than the 18.6% response rate in the younger group, although this difference did not reach statistical significance. Chemotherapy is frequently withheld from elderly patients because it is felt that the risk of toxicity is too high in this patient population. The favourable toxicity profile of gemcitabine and these interesting response rates in the elderly population suggest that this drug should be considered for future trials of chemotherapy in the elderly.

Table 7. Response rate according to patient age *

Age (years)	No. patients	Response	No response
Under 70	296	55 (18.6%)	241 (81.4%)
Over 70	32	7 (21.9%)	25 (78.1%)
Total	328	62 (18.9%)	266 (81.1%)

* American, European, South African and International studies.

Table 8. Response rate according to histologic subtype *

Subtype	No. patients	Response	No response
Squamous	136	23 (16.9%)	113 (83.1%)
Large cell	13	2 (15.4%)	11 (84.6%)
Adenocarcinoma	161	29 (18.0%)	132 (82.0%)
Mixed	9	6 (66.7%)	3 (33.3%)
Not classified	12	3 (25.0%)	9 (75.0%)
Total	331	63 (19.0%)	268 (81.0%)

* American, European, South African and International studies.

Table 9. Best response vs effective study dose intensity * †

Theoretical dose intensity	No. patients	Response	No response
< 700	19	3 15.8%	16 84.2%
700–899	37	5 13.5%	32 86.5%
900–1099	68	13 19.1%	55 80.9%
1100–1299	97	25 25.8%	72 74.2%
>1300	78	14 17.9%	64 82.1%
Total	299	60 20.1%	239 79.9%

* American, South African and International studies. † Truncated at cycle 4.

Although the results of some of the early trials suggested that gemcitabine was not active against large cell anaplastic carcinoma of the lung, an analysis of response by tumour type revealed no significant differences for any of the four major subtypes of NSCLC (Table 8).

Dose response

In the four studies reviewed above, the starting dose for gemcitabine ranged from 800 to 1,250 mg/m^2/week × 3, and in the large International study dose escalation above 1,250 mg/m^2/week was permitted in the absence of toxicity. An analysis of patients who received four or more cycles of gemcitabine in these trials suggests that dose is an important determinant for response (Table 9). The overall response rate for patients who received less than 900 mg/m^2/week was only 14.3%. For patients who received doses between 900 and 1,099 mg/m^2/week it rose to 19.1%, and it was greater than 25% for patients treated with doses from 1,100 to 1,299 mg/m^2/week. The response rate did not continue to increase with further dose escalation.

These data suggest that there is a threshold dose for gemcitabine below which very little activity is to be expected, but whether higher gemcitabine doses will be associated with higher response rates or longer response durations remains as yet undetermined. In cells, gemcitabine is phosphorylated to gemcitabine triphosphate by deoxycytidine kinase which is the rate-limiting enzyme for active metabolite formation.[1] At this time it is not known what dose of gemcitabine saturates the enzyme when the drug is administered as an intravenous bolus over

30 min. It is quite possible that the administration of higher doses of gemcitabine over this relatively short time period may not result in higher levels of the *active compound*. If this is the case, high-dose treatment may not be associated with a higher response rate.

Several phase I studies designed to assess the feasibility of administering higher doses of gemcitabine (30 min infusion weekly for 3 weeks every 4 weeks) are ongoing.[3] One study reached a maximum tolerated dose at 2,800 mg/m^2/week. Dose-limiting toxicity was seen in 3 of 5 patients and consisted of grade 4 neutropenic infection (1 patient) and reversible grade 3 transaminase elevation (2 patients). In another trial dose escalation has continued to more than 3,500 mg/m^2/week and dose-limiting toxicity has not yet been reached. Two other phase I studies are also ongoing, but these have not reached the doses of the two earlier studies. Other toxicities seen in these trials have included anaemia, thrombocytopenia, flu-like symptoms, oedema, rash, and nausea and vomiting.

Although these trials are basically phase I toxicity trials, responses are also being evaluated. The preliminary response rate appears to be approximately 20%, but this figure has yet to be validated. If the true response rate is indeed 20%, it appears to be no greater than that seen in the phase II trials of single-agent gemcitabine at more modest doses. This would perhaps support the theory that the rate-limiting enzyme deoxycytidine kinase is saturated at much lower doses of the pro-drug, and that the administration of higher doses over a short period of time does not result in higher levels of the active compound, gemcitabine triphosphate. Further pharmacokinetic studies will be necessary to answer this question.

Summary

Gemcitabine is an active, new chemotherapeutic agent with a single-agent response rate of over 20% in previously untreated patients with NSCLC. It is well tolerated, and its favourable toxicity profile suggests that it should be evaluated in combination with other agents which are known to be active against this form of lung cancer. Alternatively, gemcitabine can be considered for use as a single agent in certain patients with advanced NSCLC. The recommended schedule of administration is weekly × 3 with a 1 week break and an infusion time of 30 min. Although dose escalation studies are ongoing at several centres, there is nothing to suggest, at this time, that higher doses of gemcitabine given in this schedule will be superior to the 1,250 mg/m^2/week dose that was used in the large international study.

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