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Combination chemotherapy with gemcitabine and cisplatin in the treatment of advanced non-small cell lung cancer: preliminary results of an ongoing phase I/II study

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Collaborative phase I and II studies of the combination of gemcitabine and cisplatin in patients with advanced non-small cell lung cancer are ongoing at five centres in the UK and France. In the initial completed phase I study, 16 patients (15 evaluable) have been entered using a fixed dose of gemcitabine 1000 mg/m^2 given as a 30 min intravenous infusion weekly for 3 weeks. On the third week the gemcitabine was immediately followed by cisplatin with pre- and post-hydration. This regimen required only 1 night of hospitalization every 4 weeks. The study design was for sequential groups of patients to receive 3 dose levels of cisplatin (60 mg/m^2, 75 mg/m^2 and 100 mg/m^2) but these doses would be modified and the number of patients at any dose level could be increased if significant toxicity was observed. Three patients were to be entered at the first two dose levels and 10 patients were to confirm the maximum tolerated dose (if reached) or expand the database on toxicity at the final predetermined dose level. The major haematological toxicities were neutropenia (grade 4 in 3 patients) and thrombocytopenia (grade 3 or 4 in 5 patients) but both were of short duration and uncomplicated. Grade 3 nausea and vomiting occurred in 12 patients but was no worse than would be expected from cisplatin alone. Alopecia was not a problem (no hair loss in 10 patients and grade 1 or 2 in 6 patients) and no significant renal or neurotoxicity was seen. A phase II study using cisplatin 100 mg/m^2 in combination with gemcitabine 1000 mg/m^2 has been opened and to date 19 patients are evaluable for response. Eight (42%) have achieved partial remissions. The study is ongoing and will recruit 50 evaluable patients.

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Introduction

Metastatic or inoperable locally advanced non-small cell lung cancer (NSCLC) is incurable with current therapeutic approaches. Advances in the outcome for NSCLC patients depend on the development of new agents or new approaches to the use of existing drugs.

Only four registered cytotoxic drugs (cisplatin, ifosfamide, vindesine, mitomycin C) have been tested in large numbers of patients and have reproducible response rates > 15%.[1] All may be associated with significant toxicities. Several studies have attempted to determine whether combination regimens are superior to single agents, and although combination therapy usually produces improved response rates, this is often at the cost of increased toxicity without a significant survival benefit.[2] Chemotherapy has been compared with best supportive care (BSC) for patients with advanced disease and appears to result in a modest improvement in survival.[3,4] Although detailed quality of life assessments have not been performed in the majority of reported NSCLC chemotherapy trials, it would appear from one small study that symptomatic improvement can occur in most patients treated, even in the absence of objective responses.[5]

Currently available chemotherapy therefore appears to have a modest role in the treatment of NSCLC; but it is essential to discover new approaches with drugs having novel mechanisms of action before a major impact on survival will occur. Recent

phase II studies have confirmed the novel nucleoside analogue gemcitabine to be an active agent in the treatment of NSCLC, with response rates averaging 21% (reviewed in ref. 6). Toxicity at the dose and schedule chosen for further clinical development (1000 mg/m^2 weekly × 3) is mild and mainly comprises myelosuppression, making it an attractive agent to consider in a combination regimen. Preclinical models have demonstrated synergistic tumour cell killing when it is combined with cisplatin.[7] This synergy may result from an inhibition of DNA excision repair (a major mechanism for the development of cisplatin resistance) by gemcitabine. Gemcitabine inhibits DNA repair by inhibiting the key enzyme ribonucleotide reductase.

Based on their single-agent activities and on the promising preclinical data, a clinical trial combining gemcitabine and cisplatin in NSCLC was established. An initial phase I study examined escalating doses of cisplatin with gemcitabine. Day 15 administration of cisplatin was chosen, given the theoretical concern about the potential for nephrotoxicity of the combination. A phase II study is ongoing to examine the activity of the combination.

Patients and methods

Patients

For phase II of the study, patients were eligible with inoperable (stages IIIa, IIIb, IV), progressive, histologically confirmed NSCLC. Other entry criteria included no prior chemotherapy or radiotherapy, age range 18–75 years, bidimensionally measurable disease, WHO performance status 0–2, adequate bone marrow reserve (leucocytes > 3 × 10^9/L, platelets > 100 × 10^9/L, haemoglobin > 10 g/dl), adequate liver function (bilirubin < 2 × upper normal), AST and/or ALT < 3 × upper normal and normal renal function (normal serum creatinine and measured creatinine clearance > 60 ml/min). Exclusion criteria included concomitant medication with allopurinol or high-dose steroids (prednisolone > 10 mg/day) and the presence of CNS metastases. For the phase I portion of the study, at the lower two dose levels (but not at 100 mg/m^2), patients could have had unidimensionally measurable disease and were also eligible if they had received prior radiotherapy, providing this was not to the only site of measurable disease.

Treatment

This study was divided into two sections. In an initial phase I portion, the maximum feasible dose of cisplatin which could be combined with gemcitabine was determined. This was followed by a phase II study to determine activity using the dose chosen from the phase I portion.

Gemcitabine 1000 mg/m^2 was dissolved in 0.9% saline at a concentration of 10 mg/ml and was infused over 30 min on days 0, 7 and 14. On day 15, the gemcitabine was immediately followed by hydration (500 ml 0.9% saline over 1 h, 500 ml 0.9% saline + 20 mmol potassium chloride over 1 h, 500 ml 0.9% saline + 10 mmol magnesium sulphate over 1 h). Cisplatin (in 1000 ml 0.9% saline) was then administered over 4 h if urine output was 100 ml/h over the preceding 6 h (further prehydration and 10% mannitol were given if urine output was < 100 ml/h). In the phase I part of the study, cisplatin doses were escalated between sequential cohorts of patients, the first group receiving 60 mg/m^2. An adaptive control algorithm was used to determine the dose of cisplatin for subsequent cohorts of patients, based on the previous experience of all patients at a given dose level. The study was completed when the predetermined maximum dose of cisplatin (100 mg/m^2) was administered to the final cohort, at which level 10 patients were entered for detailed toxicity assessment. Post-hydration with 1.5 l 0.9% saline (including 20 mmol potassium chloride and 10 mmol magnesium sulphate) was given. No therapy was given on day 21. Courses were repeated every 28 days with only 1 night of hospitalization planned. Patients with response or stable disease continued therapy until progression or until a cumulative cisplatin dose of 600 mg/m^2 had been administered. Patients could be withdrawn due to unacceptable toxicity or other patient- or physician-determined reasons. Patients gave informed consent before entering the study, which followed the guidelines for good research practice and was approved by local ethical committees.

Dose modifications

During the phase I portion of the study doses were not reduced but treatment was delayed if, at the time of planned retreatment, neutrophils < 1.5 × 10^9/L and/or platelets < 100 × 10^9/L, or non-haematological toxicity (> grade 1) persisted. Patients were removed from the study if toxicities had not resolved within 3 weeks. During the phase II portion, doses of gemcitabine and cisplatin were reduced by 25% if, on the day of planned treatment, WBC = 2–2.9 × 10^9/L and/or platelets = 50–99 × 10^9/L. Therapy was omitted for counts below these levels. If creatinine clearances fell to 40–60

Table 1. Patients entered into phase I study

	No. patients
Entered	16
Gender	
Male	13
Female	3
Median age (years)	58
Performance status	
0	14
1	2
Histology	
Adenocarcinoma	3
Squamous	8
Large cell	5
Stage	
IIIa	1
IIIb	5
IV	10

ml/min, doses of both agents were reduced by 50% and were omitted for levels < 40 ml/min. Cisplatin doses were reduced by 50% for WHO neurotoxicity grade 2 and were omitted for grades 3–4.

Response assessment and toxicity monitoring

Response to therapy was assessed by standard WHO criteria after 2 courses and thereafter following each course. All response data will be validated by an independent Oncology Review Board. Toxicity was documented according to WHO grade.[8] A full blood count, biochemical screen, clotting studies, liver function tests, urinalysis (including measures of renal tubular and glomerular damage with analysis of urinary N acetyl-*B*-D glucosaminidase, alanine aminopeptidase and microalbumin) and electrocardiograph were performed regularly throughout therapy, together with weekly physical examinations and documentation of WHO performance status. Serum was also stored for assessments of gemcitabine and cisplatin pharmacokinetics.

Results

Phase I study

Sixteen patients were entered into the phase I portion of the study (characteristics given in Table 1). Sixty-two courses of chemotherapy were administered (median 3 courses for each patient, range 1–8). Two patients at the first dose level of cisplatin (60 mg/m^2) had objective tumour responses. The treatment was well tolerated at all dose levels with no life-threatening toxicity. Escalation of the dose of cisplatin was possible in sequential cohorts of patients to the planned maximum predetermined level of 100 mg/m^2. There was no evidence that the toxicity which occurred was dose related, so toxicities for all dose levels are combined for the purposes of this analysis. Only one dose of chemotherapy was omitted (for prolonged neutropenia) and no patients were removed from the study for toxicity. Dose reductions were never required.

Haematological toxicity. Neutropenia was the most frequent toxicity (grade 1, 1 patient; grade 2, 4 patients; grade 3, 2 patients; grade 4, 3 patients). Grade 3 leucopenia occurred in 2 patients but grade 4 leucopenia was never documented. Mild anaemia (grade 2, 9 patients; grade 3, 3 patients) occurred but only 4 transfusions were required. Thrombocytopenia grade 3 was documented in 2 patients and grade 4 in 1 patient. All haematological toxicity was brief and uncomplicated.

Infections. No admissions for sepsis or febrile neutropenia were necessary. Only 4 episodes of fever occurred (grade 1, 1 patient; grade 2, 3 patients), all thought to be related to respiratory infections; and therapy with oral antibiotics was associated with resolution in all instances.

Non-haematological toxicity. One patient experienced a transient rise in serum creatinine after cisplatin but no other renal toxicity was reported. WHO grade 3 nausea and vomiting was the major non-haematological toxicity observed (12 patients), occurring on the third week of therapy and being no worse than would be expected for cisplatin alone. Mild (grade 1 or 2) neurotoxicity, seen in 3 patients, resolved after completing therapy. Alopecia was not a problem: no hair loss in 10 patients, and grade 1 or 2 alopecia in 5 and 2 patients respectively.

Phase II study

On completion of the phase I study, a phase II study was initiated to assess the activity of the combination of gemcitabine 1000 mg/m^2 and cisplatin 100 mg/m^2. A secondary endpoint was to expand the database on toxicity and pharmacokinetics at this dose level. To date 25 patients have been recruited and their characteristics are given in Table 2.

Responses

Nine of the 10 patients at the top dose level in the phase I study are included in a preliminary response-

Table 2. Patients entered into phase II study

	No. patients
Entered	25
Gender	
Male	20
Female	5
Median age (years)	58
Performance status	
0	2
1	15
2	8
Histology	
Adenocarcinoma	10
Squamous	10
Large cell	5
Stage	
IIIa	1
IIIb	16
IV	8

rate analysis. One patient did not receive cisplatin during the first course of chemotherapy and was excluded from the efficacy analysis. Nineteen patients who have received 2 courses of chemotherapy are currently evaluable for response. Responses have all been assessed using serial CT scanning and 8 patients have documented partial remissions for a response rate of 42%. Seventeen patients remain on study. It is too early to comment on relapse-free or overall survival, and a detailed toxicity analysis of patients in the phase II study has not yet been made.

Discussion

Although these are preliminary results, some early conclusions can be drawn about the use of combination chemotherapy with gemcitabine and cisplatin in advanced progressive NSCLC. The first study has demonstrated that the use of three short infusions of 1000 mg/m^2 gemcitabine given weekly for 3 weeks, followed on the third week by cisplatin 100 mg/m^2, is safe and well tolerated. Only 1 night of hospitalization was necessary. The main toxicity was related to bone marrow suppression (predominantly neutropenia and, to a lesser degree, thrombocytopenia), although this was of brief duration and not associated with any episodes of septicaemia or haemorrhage. The incidence of WHO grade 3 and 4 neutropenia (33% of patients) was higher than has been seen with gemcitabine alone (22% of patients).[9] Only one dose of treatment was omitted because of toxicity so that, for the majority of patients, full protocol dose intensity could be maintained.

In the recently published phase II study of single-agent gemcitabine in NSCLC,[9] 2 patients developed acute renal failure 4 and 6 weeks after completing therapy. In both cases biopsies revealed microangiopathic haemolytic anaemia which was more likely to be related to the underlying malignancy than to the chemotherapy. Despite this, and in view of the fact that cisplatin, an agent with known nephrotoxic potential, was being combined with gemcitabine, caution was exercised during the study, with regular monitoring of renal function and measurements of glomerular and tubular damage. Only one patient experienced a transient mild rise in serum creatinine, which resolved spontaneously and did not recur with further treatment. Although the results of a detailed analysis of serial urinary enzyme and microalbumin clearance are not yet available, no patient has developed serious impairment of renal function during therapy or after follow-up.

The major subjective toxicity was nausea and vomiting, which was WHO grade 3 in the majority of patients on the day of cisplatin administration. This was usually rapidly controlled with the use of a 5-HT antagonist and dexamethasone, and never prolonged the duration of planned in-patient stay (1 night only). Vomiting was unusual on the days of single-agent gemcitabine administration; and nausea, when it occurred, was easily managed with simple oral antiemetics. The neurotoxicity of cisplatin did not appear to be exacerbated by the addition of gemcitabine, with no grade 3 or 4 neuropathy being documented.

The preliminary response rate assessment of 42% reported in this interim analysis must be interpreted with caution as the study remains open and some of the physician-reported responses have not yet been validated by the external review board. Despite this, the early results appear encouraging and suggest that the combination has significantly greater activity than either agent used alone. This may support the preclinical data which demonstrated synergistic tumour cell killing between the two compounds.[7] The combination is particularly interesting for patients with NSCLC because of its favourable toxicity profile and the requirement for only 1 night of in-patient stay each month. Unfortunately, data on relapse-free and overall survival are not yet available but will be important endpoints when a final assessment of the value of the regimen is made.

If the activity of this combination is confirmed when the study is completed, future strategies to optimize the relative timing of administration of the two agents will be necessary. It is still unclear from preclinical models whether the gemcitabine should precede or follow the cisplatin, and clinical studies have already been established to examine alternative scheduling. Once the optimal schedule of this novel combination is determined, a logical development would be to compare it with a "standard" regimen in a randomized phase III study and to incorporate quality of life assessments as an integral part of the monitoring of both arms.

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