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Clinical report

Phase I study of gemcitabine in combination with cisplatin, 5-fluorouracil and folinic acid in patients with advanced esophageal cancer

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The prognosis for advanced esophageal carcinoma is poor with a median survival of 9–12 months and 5-year-survival rate of 10–20%. Combination chemotherapy with cisplatin and 5-fluorouracil (5-FU) is considered to be the standard therapy, but has a high potential of side effects and is usually not given on an ambulatory basis. This phase I study was designed to find the maximum tolerated dose (MTD) of weekly cisplatin in combination with standard doses of gemcitabine (1000 mg/m^2, 30 min) and 5-FU (750 mg/m^2, 24 h)/folinic acid (200 mg/m^2, 30 min). All drugs were to be given on a day 1, 8, 15 and 22 of a 6-weekly cycle in an outpatient setting. Nineteen chemonaive patients with inoperable stage IIa, III and IV squamous cell carcinoma and adenocarcinoma of the esophagus were enrolled into the study. Eight, six and five patients were enrolled at cisplatin dose levels 0 (20 mg/m^2), I (25 mg/m^2) and II (30 mg/m^2), respectively. One hundred and eighty-one out of 187 treatments (55 cycles) were given on an outpatient basis. The dose-limiting toxicities of this schedule were leukopenia and thrombocytopenia. Other side effects were mild. Dose level II (30 mg/m^2) was defined as the MTD for cisplatin when used in this combination and schedule. Partial responses were observed in 10 of the 19 enrolled patients. The side effect profile seen in this study in combination with the preliminary evidence of efficacy justifies further testing in a phase II setting with a cisplatin dose of 25 mg/m^2 and offers a treatment option for patients in an outpatient setting. [© 2002 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, adenocarcinoma, cisplatin, gemcitabine, esophageal cancer, squamous cell carcinoma.

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Introduction

The incidence of esophageal cancer continues to rise, due to a rapid increase in the incidence of adenocarcinoma of the esophagus and gastro-esophageal junction. In both the US and Europe, adenocarcinomas now account for over 50% of newly diagnosed cases.[1]

The prognosis for patients with locally advanced or metastatic esophageal cancer is poor, as indicated by a median survival of 9–12 months and a 5-year survival of 10–20%.[2] More than 90% of patients will die from their disease. For locoregional disease, primary treatment modalities are surgery alone or combination strategies with chemotherapy or radiation therapy.[3–6] Surgery provides the only chance of cure and is the treatment of choice for local, regionally confined esophageal cancer. However, the results are poor, with 5-year survival rates of only 6–24% in western countries.[3] Moreover, the majority of patients with advanced locoregional disease will ultimately develop metastases and become candidates for palliative chemotherapy.

Traditionally, the most effective chemotherapeutic agents in the treatment of this disease have been cisplatin, 5-fluorouracil (5-FU) and mitomycin C.[7] Combination chemotherapy leads to partial responses in 25–50% of cases and rare complete responses, including a 35% response rate with cisplatin/5-FU combination therapy.[8] Currently, cisplatin in combination with 5-FU is most widely used for the treatment of both squamous cell carcinoma (SCC) and adenocarcinoma of the esophagus,[7] although other drugs like paclitaxel and irinotecan have recently shown favorable response rates, both

Table 1. Dose escalation

Dose level	Cisplatin [mg/m^2 [a](1 h)]	Gemcitabine [mg/m^2 (30 min)]	FA [mg/m^2 (30 min)]	5-FU [mg/m^2 (24 h)]
0	20	1000	200	750
I	25	1000	200	750
II	30	1000	200	750

[a]Each dose escalation step = 5 mg/m^2. All treatments were administered on days 1, 8, 15 and 22 with a therapy break on days 23–42 of a 42-day cycle.

as single agents and in combination with cisplatin.[9–11] However, the responses to chemotherapy are usually short lived and the toxicity of these cisplatin-based therapies is often substantial, particularly in the palliation of metastatic disease. Therefore, there is an urgent need to identify new less toxic treatments either for use in combination with existing agents, i.e. cisplatin and 5-FU, or to replace existing therapeutic agents, in the treatment and control of this disease.

Gemcitabine (Gemzar) is an attractive candidate for combination therapy due to its multiple and novel mechanisms of action,[12,13] and its mild toxicity profile. There is preclinical evidence that gemcitabine modulates 5-FU activity,[14] as well as synergistic preclinical and clinical activity with cisplatin.[15–17] Recently, our group has demonstrated that gemcitabine (1000 mg/m^2) in combination with 5-FU (750 mg/m^2) plus folinic acid (FA) administered on days 1, 8, 15 and 22 of a 42-day schedule is effective and well-tolerated in the palliative, outpatient treatment of patients with advanced pancreatic cancer.[18] In reflection of this data, we wanted to add cisplatin as a cornerstone of chemotherapy in esophageal cancer to this regimen. In order to define an outpatient schedule for this novel treatment combination, a phase I study was conducted, in chemonaive patients with advanced adenocarcinoma or SCC of the esophagus, to determine the maximum tolerated dose (MTD) of cisplatin when administered in combination with constant doses of gemcitabine, 5-FU and FA.

Patients and methods

Patient selection

Patients were eligible for entry if they had histologically confirmed non-resectable, stage II (proximally located tumor), III or IV SCC or adenocarcinoma of the esophagus, had not received prior chemotherapy, were >18 years of age, had a Karnofsky performance status $\geqslant 60\%$ as well as adequate bone marrow, liver and renal function. Patients may have had a prior malignancy if they had been curatively treated and had been relapse free for >3 years.

Patients were excluded if they had an active infection, liver enzymes (ALT/AST) >3 times the upper reference value (URV), bilirubin $\geqslant 1.5$ times the URV or if their creatinine clearance was <60 ml/min. Increased calcium levels, pregnancy or breast-feeding and complications that needed acute intervention were also reasons for exclusion.

The study was approved by the local ethics committee and all patients provided signed informed consent.

Study design

This was a single center, phase I, dose-finding study. Cisplatin was administered in escalating steps in an attempt to determine the MTD of cisplatin that could be administered in combination with gemcitabine, FA and 5-FU in an outpatient setting.

Drug administration

Gemcitabine 1000 mg/m^2 was administered over 30 min i.v., followed by FA 200 mg/m^2 (30 min) i.v. and 5-FU 750 mg/m^2 as a 24-h infusion, via a portable battery-driven pump (Walkmed 350) as previously described.[18] The cisplatin dose was escalated in steps of 5 mg/m^2 starting at dose level 0 with 20, 25 and 30 mg/m^2 at dose levels I and II, respectively (Table 1). All treatments were administered on days 1, 8, 15 and 22 followed by 2 weeks rest, days 23–42. Each cycle lasted for 43 days. All patients received antiemetic prophylaxis with a 5-HT$_3$ receptor antagonist and 12 mg dexamethasone before the cisplatin administrations.

It was anticipated that each dose level would contain three to six patients depending on when dose-limiting toxicity (DLT) occurred. The MTD was predefined as the highest level at which the incidence of DLT, defined as hematological WHO toxicity grade $\geqslant 3$ lasting for more than 5 days, febrile neutropenia, non-hematological toxicity WHO grade $\geqslant 3$, did not exceed 1 in every three patients or 2 in every six patients within the first 2 cycles of therapy

(3 months). In case of leukopenia WHO grade 3 and/or thrombocytopenia WHO grade 3 within a cycle, cisplatin was reduced by 25%, while gemcitabine, FA and 5-FU were given at full dose. In case of WHO grade 3 non-hematological toxicity (except nausea/vomiting and alopecia) the cisplatin dose was reduced by 50%. For hematological toxicity WHO 4, thrombocytopenia WHO grade 3 and/or non-hematological toxicity grade 4, further treatment was halted for the remainder of the cycle.

Toxicity assessments

Toxicity was evaluated according to WHO toxicity criteria. Total white blood cell, platelet and neutrophil counts, and non-hematological side effects were evaluated prior to every treatment. Karnofsky performance status and weight were assessed at the start of each cycle.

Evaluation of response

Pre-treatment staging was established by barium esophogram, computed tomography (CT) scans of the chest, endoscopy of the esophagus and bronchoscopy (if the tumor was located proximally).

Tumor response was evaluated by CT scan and/or endoscopy of the esophagus after every cycle according to WHO guidelines. If the patient exhibited stable disease therapy continued, if there was evidence of tumor regression the possibility of surgical resection was investigated. If there was confirmed disease progression, the patient was excluded from the study and underwent chemoradiotherapy. No patient was to receive more than 4 cycles of therapy. Patients who successfully completed 4 cycles of therapy were considered for either surgery or chemoradiotherapy, depending on disease status.

Results

Patient characteristics

From June 1999 to July 2000, 19 patients were enrolled into the study. Patient characteristics are listed in Table 2. The majority (78%) of patients were male. SCC was the predominant histological type. No patient had received prior chemotherapy. All 19 patients were evaluable for response.

Table 2. Patient baseline characteristics

	N
No. patients enrolled	19
No. evaluable patients	19
Median age (years) [range]	61 [46–71]
male	14
female	5
Median Karnofsky performance status (%) [range]	80 [70–90]
Histiological type	
squamous	15
adenocarcinoma	4
Stage AJCC	
IIA[a]	1
III	11
IV	7

[a]Not operable due to the proximal localization.

Table 3. Summary of the therapy cycles in relation to the dosage level

	Dose level		
	0	I	II
No. patients	8	6	5
No. cycles	23	17	15
No. planned drug administrations	90[a]	68	60
No. drug administrations	82	58	47
No. patients with dose reductions	5	4	4
Cisplatin dose reduction to 75%	10/82	15/58	21/47
Cisplatin dose reduction to 50%	1/82	2/58	3/47
All drugs postponed	8	10	13
Number of patients with omissions	6	5	4

[a]One patient in stable disease refused further treatment after 14 out of 16 scheduled drug administrations.

Therapy administrations

The median number of treatment cycles administered per patient was 3 for each dose level. The total number of treatment cycles initiated was 55. A total of 187 weekly treatments were administered, 181 (97%) on an outpatient basis. There were 11 cisplatin dose reductions (12%) in five out of eight patients at dose level 0, 17 cisplatin dose reductions (25%) in four out of six patients at dose level I and 24 cisplatin dose reductions (40%) in four of five patients at dose level II. There were eight total therapy omissions (9% of intended drug administrations) in six out of eight patients at dose level 0 as well as 10 omissions (15%) in five out of six and 13 total therapy omission (22%) in four of five patients at dose levels I and II, respectively (Table 3).

Three patients were entered into the study at dose level 0. There were no DLTs in any of the three patients and the cisplatin dose was escalated to *dose*

Table 4. Summary of therapy cycles with WHO grade 3/4 toxicities

Dose level	Cycles	Leukopenia	Thrombopenia	Anemia	Liver enzymes	Creatinine
0	23	5/0	3/1	1/0	1/0	0/0
I	17	4/0	7/1	0/0	1/0	0/0
II	15	10/1	5/4	1/0	0/0	0/0

Table 5. Summary of patients with WHO grade 3/4 toxicities

Dose level	Patients	Leukopenia	Thrombopenia	Infection	Nausea	Alopecia
0	8	3/0	2/1	0/0	0/0	0/0
I	6	3/0	4/1	0/0	0/0	1/0
II	5	3/1	1/4	1/0	0/0	2/0

level I (Table 1) for the next three patients. Dose-limiting WHO grade 4 thrombocytopenia lasting for more than 5 days occurred in the second cycle in one patient and three further patients were enrolled at this dose level. All six patients received a total of 17 cycles with 58 weekly drug administrations (Table 3). WHO grade 3 thrombocytopenia and leukopenia lead to dose reductions and omissions in 17 of the 68 planned weekly therapy administrations. No further patients experienced DLT at this dose level.

Consequently, the next three patients were enrolled at *dose level II*. One patient (out of three) experienced febrile leukopenia and grade 4 thrombocytopenia during the second cycle. Two more patients were enrolled simultaneously. One patient presented with grade 4 leukopenia and thrombocytopenia after the second drug administration. A few days later he suffered from acute convulsions and developed hemiparesis (with a normal platelet count), probably representing a stroke and subsequently died. In summary, two out of five patients at this dose level experienced DLTs during the first 2 cycles. Further treatments were given at a reduced dose of cisplatin (75%), but several incidences of grade 3 and 4 hematotoxicity were observed, mostly as the result of cumulative toxicity. In total, less than 50% of treatment applications could be administered at the intended cisplatin dose level II.

Analysis of the therapy administered at dose level I showed a significantly decreasing rate of administration of the intended full-dose of cisplatin, a further five patients were enrolled at *dose level 0*. Overall, 82 drug administrations were made to a total of eight patients, over at 23 cycles, at a cisplatin dose of 20 mg/m^2. Ten and one of the 82 administered cisplatin doses were reduced by 25 and 50%, respectively. There were eight therapy omissions, but 71 out of the 90 of intended therapy administrations were given at 100% dose level.

Toxicity

Myelotoxicity was the most common toxicity encountered using this therapy combination. The hematological toxicities observed at all three dose levels are summarized in Tables 4 and 5. Twenty-two percent of cycles at dose level 0 were associated with WHO grade 3 leukopenia; 13% and 4.3% of cycles were associated with WHO grade 3 and 4 thrombocytopenia, respectively. The percentage of cycles associated with WHO grade 3/4 thrombocytopenia rose to 60% at dose level II, whilst the incidence of WHO grade 3/4 leukopenia rose to 73% of cycles (Table 4). Except one patient with fatal toxicity at level II, non-hematological toxicities were surprisingly mild. Temporary and self-limited elevation of liver enzymes (AP and AST/ALT grade 3) were observed in one patient each at dose level 0 and I. One more patient experienced febrile neutropenia. Other symptomatic toxicity except for alopecia did not exceed WHO grade 2. Alopecia was almost universal, and reached grade 3 in three patients (Table 5). Anemia WHO grade $\geqslant$3 was reported in two out of 55 cycles only (Table 4). One patient received two transfusions. No WHO grade $\geqslant$3 nausea was reported for any cycle in these patients on antiemetic prophylaxis.

Response

Partial responses to this chemotherapy regimen according to WHO criteria were observed in 10 (52.6%). out of 19 patients (Table 6). In four out of seven patients with metastatic disease, tumor regression of more than 50% was confirmed by CT scan. Out of the 12 patients with locally advanced, non-metastatic tumors, six further partial responses were observed by evaluation via endoscopic ultrasound and/or CT scan, respectively. Depending on disease

Table 6. Response status after therapy

Response	No. patients
Partial response	10
Minor response	1
Stable disease	2
Progressive disease	5
Early death	1

status, patients were to receive further treatment modalities, either surgical resection (two patients) or consolidating chemoradiation of the primary tumor lesion (eight patients). While the response rate resulted from chemotherapy regimen alone, the median duration of response for the therapeutic sequence (chemotherapy of maximum 4 cycles, preceding either surgery or chemoradiation) was 34+ weeks (range 26 to 54+).

One more patient achieved a minor response while two patients had stable disease, one at dose level I (duration 20 weeks) and one at dose level 0 (duration 6 weeks). Five patients experienced progressive disease and there was one early death.

More specifically, at *dose level 0*, three out of eight (37.5%) patients experienced partial remissions after 4, 4 and 2 cycles of therapy. After completion of the protocol-defined 4 cycles of chemotherapy, two patients received radiochemotherapy and one patient underwent surgery (R0 resection) after 2 cycles and absolved.

At *dose level I*, three out of six (50%) patients experienced partial remissions after 4 cycles of chemotherapy and all of them went on to receive chemoradiotherapy.

Finally, at *dose level II*, four of five (80%) patients experienced partial remission after 4, 4, 3 and 3 cycles of chemotherapy. One of these patients underwent R1 resection (after 3 cycles) and three went on to receive radiochemotherapy. As stated previously, one patient at this dose level died after two therapy administrations.

Discussion

The present study has demonstrated a MTD for cisplatin of 30 mg/m^2 in combination with gemcitabine (1000 mg/m^2), 24-h infusion 5-FU (750 mg/m^2) and FA (200 mg/m^2). At this dose level, dose reductions or omissions due to toxicity according to protocol occurred in more than 50% of intended treatment applications. As a consequence, the recommended cisplatin dose for a further phase II study is dose level I (25 mg/m^2). However, it should be pointed out that even at this dosage there was evidence of cumulative hematotoxicity as indicated by the decreasing rate of administration of the intended full-doses of cisplatin. The rate of full-dose cisplatin administrations decreased from 72% (32 of 44) during the first two cycles to 41% (nine of 22) during cycles 3 and 4. Furthermore, all cisplatin omissions and 12 out of 17 necessary dose reductions occurred at the third or fourth application (day 15 and 22) of each cycle at this dose level. In contrast, there was no further decrease in cisplatin dose level of 20 mg/m^2 when the first two cycles (79% of the full dose rate) were compared with the remaining cycles (78% of the full dose rate). Regarding other than hematological toxicity, the treatment regimen was tolerated without major side effects.

Although efficacy was not the primary endpoint in this phase I setting, a partial response rate of 52.6% is encouraging for a phase I study and equivalent to the highest previously reported responses for esophageal cancer.[19] Despite the limitations of a small patient sample, this is noteworthy, because the treatment efficacy of this disease remains so poor and because of a previous report that single-agent gemcitabine is not active in esophageal cancer.[20] In contrast, recently presented preliminary data from another small series of 19 patients with advanced esophageal carcinoma showed a response rate of 47% for standard dosage gemcitabine in combination with FA and bolus 5-FU.[21] This remarkable result might be related to the fact that all patients evaluable for response had adenocarcinoma which seems to be associated with higher response rates than SCC of the esophagus. The same response rate was observed in a phase II trial including 17 patients with esophageal cancer receiving weekly gemcitabine (800 mg/m^2) and biweekly cisplatin (50 mg/m^2). However, toxicity of this schedule was remarkable with grade 3/4 leukopenia in 64% and thrombopenia in 58%, respectively, for the whole series of patients with either esophageal or gastric cancer.[22]

The application of chemotherapy on days 1,8,15 and 22 of a 42-day schedule was chosen to improve quality of life, by allowing the patients 3 weeks (days 23–42) without therapy on a treatment schedule with purely palliative intent. Our experience with this regimen in pancreatic cancer convinced us that this 3-week therapy break is highly appreciated by the patients facing a limited life expectancy.

The promising efficacy achieved in this study, however, coupled with the possibility of resections in a number of patients, may lead to a different schedule, e.g. split course with therapy on days 1, 8, 22 and 29 with omission on days 15 and 29,

for patients with non-metastatic disease in an neoadjuvant setting, as this might allow higher dose intensities and a shift from a palliative to a curative treatment intent.

In conclusion, this novel combination with cisplatin, gemcitabine (1000 mg/m^2), 24-h infusion of 5-FU (750 mg/m^2) and FA (200 mg/m^2) on days 1, 8 and 15 on an 42-day schedule provides a safe and well-tolerated regimen, which can be administered on an outpatient basis. With a partial remission rate of more than 50% (all dose levels together), it seems to have efficacy comparable to other schedules for the treatment of advanced esophageal cancer, whether squamous cell or adenocarcinoma. As a consequence, a phase II trial has been initiated at a cisplatin dose of 25 mg/m^2, to measure response rate, median survival and clinical outcome benefit (weight improvement, performance status improvement, pain reduction if any and changes in analgesic consumption) in a similar patient group.

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