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Gemcitabine and Cisplatin for patients with metastatic or recurrent esophageal carcinoma: A Southwest Oncology Group study

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Summary

Purpose: Experimental data, both *in vivo* and *in vitro*, suggest that the combination of gemcitabine and cisplatin acts synergistically. Within the Southwest Oncology Group, we designed a Phase II trial to test this chemotherapy combination for patients with esophageal cancer. *Experimental design*: Patients with metastatic or recurrent esophageal cancer were treated with gemcitabine 1000 mg/m^2 on days 1, 8, and 15, and cisplatin 100 mg/m^2 on day 15. Cycles were repeated every 28 days. The statistical endpoint was overall survival. *Results*: Sixty-four eligible patients were accrued from 37 institutions. Twenty-six percent of patients had prior chemotherapy. The treatment was generally well-tolerated, with the most common toxicity being neutropenia in 31% of patients. All 64 patients have died. Survival at 3 months was 81%, and at 1 year was 20%. Median survival was 7.3 months. *Conclusions*: This regimen is tolerable palliative option for patients with metastatic esophageal cancer.

Introduction

Patients with metastatic or recurrent esophageal cancer have a very poor prognosis. Chemotherapy is not able to cure this advanced disease, and it cannot predictably prolong survival. The rationale for administering chemotherapy to patients with metastatic disease is palliation of distressing symptoms.

Relatively few chemotherapy agents are effective against esophageal cancer, and therefore any new agents with possible activity in this disease warrant exploration. Typical chemotherapy agents for this disease and their response rates as single agents include cisplatin – 20% [1], 5 – fluorouracil – 16% [2], paclitaxel – 32% [3], and mitomycin-C – 18%–30% [4], irinotecan – 33% in gastric cancer (5), and docetaxel – 18% in chemotherapy-naïve patients [6]. Combination chemotherapy yields slightly higher response rates.

Unfortunately, a good response rate does not necessarily translate into improved survival. The median survival of patients diagnosed with metastatic disease is 4–8 months [7]. In the most recent experience of the Southwest Oncology Group utilizing a Phase II agent, the estimated median survival in this population was 3 months [8].

Gemcitabine (difluorodeoxycytidine), an analog of cytosine arabinoside (ara-C), is a pyrimidine antimetabolite [9]. The mechanism of action of gemcitabine has been well characterized. Gemcitabine is activated by deoxycytidine kinase to difluorodeoxycytidine monophosphate (dFdCMP). Then, dFdCMP is further metabolized to difluorodeoxycytidine diphosphate (dFdCDP) and triphosphate (dFdCTP) which, when incorporated into DNA, results in chain termination. In comparison to ara-C incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates

intracellularly to a greater degree than ara-C. This may account, in part, for its different spectrum of preclinical and clinical activity. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis.

The favorable toxicity profile of gemcitabine does not overlap with that of cisplatin, and the two drugs have differing mechanisms of action as well. Cisplatin is a cycle-specific agent that acts by binding to DNA and produces DNA crosslinks. Gemcitabine is a phase-specific agent that inhibits excision repair of cisplatin-damaged DNA [10].

Experimental data, both *in vitro* and *in vivo*, suggest that the gemcitabine–cisplatin combination should act synergistically. This effect is dependent on the schedule of administration. Synergism was observed in a wild-type cell line and in a cisplatin-resistant cell line, but not in a gemcitabine-resistant cell line. It is likely that previous incorporation of gemcitabine to a certain extent into DNA is necessary to achieve an interaction with cisplatin, and that the synergism that occurs is largely because of inhibition of cisplatin-induced DNA repair [11,12].

Based on this potential synergism, we designed a Phase II trial of cisplatin and gemcitabine for patients with metastatic or recurrent esophageal cancer, conducted within the Southwest Oncology Group (S9801). A previous Southwest Oncology Group trial in this disease site yielded median survival of 3 months. Although response has been the traditional standard for evaluation of Phase II agents, it is a difficult endpoint to accurately assess in diseases with poor survival, due to rapid patient deterioration prior to planned timing of scans, and due to increased reluctance of institutions to schedule expensive scans. Thus, in recent years the Southwest Oncology Group has begun designing Phase II trials based on survival endpoints. For this study, the primary objectives were to assess overall survival in these patients, and to assess the toxicities of this regimen.

Methods

Eligibility criteria

Patients were required to have biopsy-proven squamous cell carcinoma or adenocarcinoma of the esophagus or GE junction. Eligible patients included those who were newly diagnosed with metastatic disease, or those with local or metastatic recurrence of disease. Patients could have measurable or evaluable disease. Patients could not have had prior treatment for metastatic or recurrent disease; they were allowed to have had prior chemotherapy or radiation if administered in the neoadjuvant setting at initial diagnosis. If previously treated, there had to be at least a 3-month interval between the last day of cisplatin and registration to this study. Patients were not allowed to have received prior gemcitabine. At least 28 days must have elapsed since completion of any other previous treatment. Southwest Oncology Group Performance Status of 0–2 was required, and the following pretreatment laboratory parameters had to be fulfilled: granulocyte count >1500 /μl, platelets $>100{,}000$ /μl, serum creatinine $<2\times$ the institutional upper limit of normal, a creatinine clearance >60 ml/min, bilirubin $<2\times$ institutional upper limit of normal, and SGOT or SGPT $<2.5\times$ institutional upper limit of normal, or $<5\times$ institutional upper limit of normal if the liver was involved with tumor. No prior malignancies were allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years. Patients could not have serious concomitant systemic disorders or active central nervous system metastases. Patients were informed of the investigational nature of the study and signed written informed consent in accordance with institutional and federal guidelines.

Treatment plan

Gemcitabine 1000 mg/m^2 IV over 30 min was administered on days 1, 8, and 15, followed by a 1-week rest. Cycles were given q 28 days. Cisplatin 100 mg/m^2 IV over 90 min was administered on day 15 of each 28-day cycle, after the gemcitabine had been given. Appropriate antiemetics were given prior to each chemotherapy treatment. Prehydration for the cisplatin was 1500 cc of normal saline plus 20 mEq potassium chloride followed by 12.5 mEq mannitol IV. push. Then, the cisplatin was administered, followed by 1000 cc normal saline.

The protocol specified dose modifications in the event the patient should experience a specific toxicity. Dosage modifications were dictated if a patient experienced any of the following hematologic toxicities: if the absolute granulocyte count nadir was 1000–1499 or if the platelet nadir was

50,000–99,999, the gemcitabine dose was changed to 500 mg/m^2 and the cisplatin dose to 50 mg/m^2; if the granulocyte nadir was 0–999 or if the platelet nadir was <50,000, no chemotherapy was given until the granulocyte count returned to >1000 and the platelets were >50,000, and then the patients were treated at the half/dose level. If the blood counts had not recovered sufficiently after holding treatment for two consecutive weeks, the patient was removed from protocol treatment. If patients completed a 3-week cycle at full doses without nonhematologic toxicity >grade 1, and if absolute granulocyte count was always greater than 1500 and platelets were always greater than 100,000, then the gemcitabine dose was escalated by 25%.

Modifications were also dictated for nonhematologic toxicities. On the day of scheduled treatment with cisplatin, patients received full dose if the creatinine clearance was >60 ml/min, or 50 mg/m^2 if the creatinine clearance was 40–59 ml/min, or received no further treatment if the creatinine clearance was <40 ml/min. Cisplatin was decreased to 50 mg/m^2 for grade 2 peripheral neuropathy, and discontinued for grade 3 neuropathy. The cisplatin was decreased to 75 mg/m^2 for Grade 3–4 nausea and vomiting.

Criteria for removal from the protocol treatment were progression of disease, unacceptable toxicity, delay of greater than 2 weeks beyond the planned treatment date, or the patient's request.

Statistical considerations

The primary objective of this study was to evaluate the 3-month survival rate in patients with esophageal cancer treated with gemcitabine and cisplatin. Based on the experience of the Southwest Oncology Group in SWOG 9339, in which patients with metastatic esophageal cancer were treated with topotecan 1.5 mg/m^2 weekly × 4, every 6 weeks, the estimated median survival in this population was 3 months [8]. It was assumed that the gemcitabine/cisplatin regimen would be of interest if the 3-month survival were 70% or better. Median survival and the 3-month survival rate were estimated using the Kaplan–Meier method.

Results

Patient characteristics

The Southwest Oncology Group initiated this trial on April 1, 1998. Between that date and June 15, 1999, 73 patients were accrued from 37 institutions. Nine patients were ineligible. Reasons for ineligibility were: inadequate documentation of baseline eligibility requirements (five patients), radiation therapy to a metastatic site prior to study entry (one patient), absence of metastatic or recurrent disease (two patients), and inadequate creatinine clearance (one patient). Patient characteristics for the 64 eligible patients are described in Table 1. Sixty-one patients were male, and the median age was 57. Fifty-two patients (81%) had adenocarcinoma, ten patients (16%) had squamous cell carcinoma, and two patients (3%) had other pathology (adenosquamous, and undifferentiated). Twenty-nine patients had newly diagnosed metastatic disease, and thirty-five had recurrent disease. Thirty-two patients had measurable disease, and thirty-two had nonmeasurable disease. Seventeen points (26%) had prior chemotherapy, nineteen (30%) had prior radiation, and twenty-two (35%) had prior surgery. The prior chemotherapy regimens used were: cisplatin/5-fluorouracil – 11 patients; carboplatin/paclitaxel – 3 patients; cisplatin/ paclitaxel – 1 patient; carboplatin/5-fluorouracil/paclitaxel – 1 patient; and unknown – 1 patient.

Table 1. Patient characteristics

No. of eligible patients	64
Age	
Median	57
Range	33–77
Sex	
Males	61 (95%)
Females	3 (5%)
Histology	
Adenocarcinoma	52 (81%)
Squamous cell	10 (16%)
Other	2 (3%)
Disease Status	
Metastatic	29 (45%)
Recurrent	35 (55%)
Prior Therapy	
Chemotherapy	17
Platinum-based	16
Not specified	1
Radiation	19
Surgery	22
None	6
SWOG performance status	
0	30 (47%)
1	29 (45%)
2	5 (8%)

Thirty patients (47%) had a performance status of 0, 29 (45%) had a performance status of 1, and 5 (8%) had a performance status of 2.

Toxicity

Patients received the following total cycles of chemotherapy: 1–2 cycles – 36 patients; 3–4 cycles – 14 patients; 5–6 cycles – 12 patients; 7–8 cycles – 1 patient, and >8 cycles – 1 patient.

Thirty-seven patients required a reduction of the dose of gemcitabine, and four patients required a reduction in cisplatin. The primary reason for the dose reductions was neutropenia. However, none of the patients experienced febrile neutropenia, or required hospitalization. In virtually every case the granulocytes recovered within a short period of time without sequelae. Two patients were given a dose escalation of the gemcitabine.

Patients came off of protocol treatment for the following reasons: toxicity – eight patients (four – nausea/vomiting, one – tinnitus, one – hearing loss, one – nephrotoxicity, and one – weight loss); refusal – eight patients; progression of disease – thirty-seven patients; death while on active treatment – six patients (described below); and other reasons – five patients (two patients had medical problems not related to chemotherapy which delayed treatment >2 weeks; one patient had stable disease but no symptom relief and wanted other treatment; one patient had an excellent response and so his physician switched him to more aggressive chemoradiation; and one patient – unknown.) There were no major protocol deviations.

Six deaths occurred during active treatment. One was considered definitely related to treatment: renal failure likely related to the cisplatin. One death was possibly related to treatment: a patient with a history of cardiac disease and hypertension had a cardiac arrest 5 days after his first chemotherapy treatment (no neutropenia). Four deaths were considered to be unrelated to the treatment: three were due to disease progression, and one occurred as a complication of an ERCP done to remove a biliary stent in a patient who was clinically improving on chemotherapy.

Toxicities are summarized in Table 2. The most common grade 3 or 4 toxicities that patients developed were: neutropenia – 31%, leukopenia – 23%, nausea – 17%, vomiting – 11%, thrombocytopenia – 11%, anemia – 11%, fatigue – 8%, and dehydration – 8%.

Table 2. Chemotherapy toxicity

Toxicity	Grade 3/4 (%)
Neutropenia	31
Leukopenia	23
Nausea	17
Vomiting	11
Thrombocytopenia	11
Anemia	11
Fatigue	8
Dehydration	8

One death due to renal failure, related to treatment; One sudden death, possibly related to treatment; Eight patients discontinued treatment due to toxicity.

Survival

All 64 patients have died, and have been included in the survival analysis. Median survival is 7.3 months (95% CI 5.1–8.8). Survival at 3 months is 81% (95% CI 72–91) and at 1 year is 20% (95% CI 10–30). See Figure 1.

Median time to treatment failure (disease progression or discontinuation of treatment for any reason) was 2.5 months, with 28% still failure-free at 4 months.

Discussion

Treatment of metastatic or recurrent esophageal cancer generally begins with a discussion of the possible goals of therapy. Patients must be told that the disease is not curable, and that chemotherapy does not predictably prolong life. It is most commonly used with palliative intent.

Relatively few chemotherapy agents are effective against esophageal cancer, and therefore any new agent with possible activity in this disease warrants exploration. The most commonly used agents have been cisplatin, 5-fluorouracil, mitomycin-C, paclitaxel, and more recently irinotecan, and to some extent docetaxel.

The combination of cisplatin and 5-fluorouracil is one of the most highly used palliative regimens, yielding a response rate of about 35%, and median survival of 6–8 months [13]. However, the numerous side effects of cisplatin (nausea, ototoxicity, nephrotoxicity, and myelosuppression) and 5-fluorouracil (mucositis and diarrhea) limit their usefulness in debilitated patients.

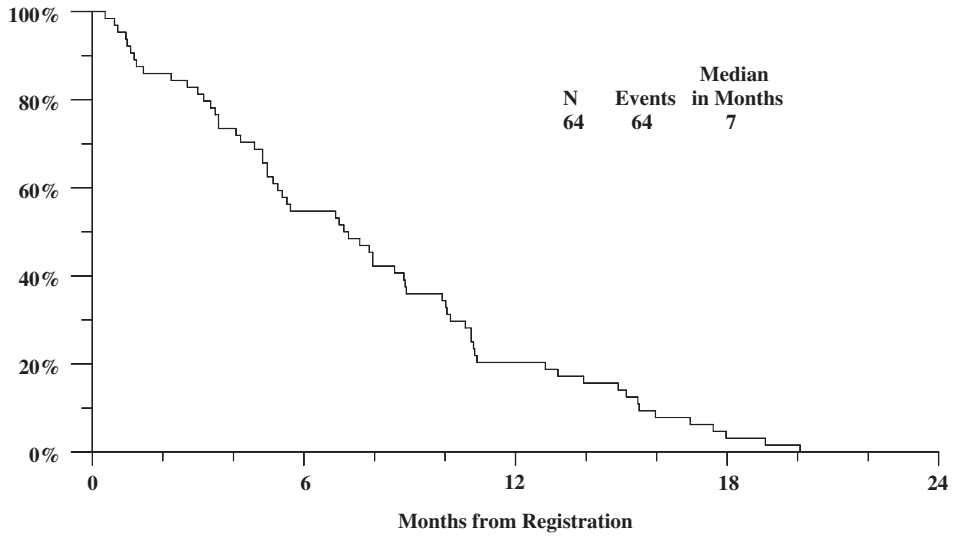

Figure 1. Survival.

Cisplatin and paclitaxel have been combined in Phase I studies, resulting in a response rate of approximately 50% [14,15]. Survival data was not available in these trials. When 5-fluorouracil was added to the cisplatin/paclitaxel combination for 61 patients with esophageal cancer, major responses were seen in 48% of patients [16]. Median survival was 10.8 months. Toxicity was considered severe but manageable, with 82% of patients experiencing grade 3 or 4 toxicities. Therefore, the same authors removed the 5-fluorouracil from the combination, and conducted a Phase II trial for 38 chemo-naïve patients with metastatic esophageal cancer [17]. Response rate was 44% and median survival was 6.9 months. However, there were four treatment-related deaths from this aggressive regimen (paclitaxel 250 mg/m^2 later reduced to 200 mg/m^2, and cisplatin 75 mg/m^2).

Gemcitabine is a relatively new agent currently undergoing evaluation for its potential activity in esophageal cancer. Single-agent gemcitabine was administered to 21 patients with chemotherapy-naïve metastatic esophageal cancer [18]. The drug was administered at a dose of 1250 mg/m^2 over 30–60 min on days 1, 8, and 15, followed by 1 week of rest, up to a maximum of six cycles. Grade 3/4 toxicities in 19 evaluable patients were granulocytopenia – 21%, and anemia – 10%. No responses were seen in 17 evaluable patients. Therefore, because of the previously mentioned synergism observed *in vitro* between gemcitabine and other agents, the possible role for gemcitabine in esophageal cancer may be in combination therapy.

Some trials have been conducted using gemcitabine in combination with other chemotherapy agents. Early data has been reported in abstract form on the combination of gemcitabine and 5-fluorouracil [19]. A Phase II trial was designed based on preclinical evidence of sequence-dependent synergy with this combination. Twenty-three patients with metastatic or advanced esophageal cancer were treated with gemcitabine 1000 mg/m^2, 5-fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Prior chemotherapy was allowed. Toxicity was mild. Thirty percent of patients experienced grade 3 hematologic toxicity. Sixty percent developed non hematologic grade 3 toxicities, such as diarrhea, nausea, vomiting, infection, and stomatitis, much of which was probably related to the 5-fluorouracil. The response rate in 22 evaluable patients was 32%. Although the trial is small, the early results are promising.

Gemcitabine has also been combined with paclitaxel in a Phase I trial for solid malignancies [20]. Eighteen patients with stage IV malignancies were treated with paclitaxel 150 mg/m^2 over 3 h every 21 days, and gemcitabine was given on days 1 and 8, in three separate dose-escalating cohorts (800, 900, and 1000 mg/m^2 over 15 min). Two of the patients had esophageal cancer. The dose-limiting toxicity was neutropenia, and the recommended starting dose for future trials was gemcitabine 900 mg/m^2. Four of the

patients (22%) had an objective response, all of whom had either transitional cell or squamous cell carcinoma.

Sequence-dependent pharmacokinetic and pharmacodynamic interactions have been observed for the combination of gemcitabine and cisplatin [21]. Forty-one patients with a variety of solid tumors were treated with one of four schedules: gemcitabine 800 mg/m^2 on days 1, 8, and 15 administered either 4 or 24 h before cisplatin 50 mg/m^2 on days 1 and 8, or cisplatin administered either 4 or 24 h before gemcitabine. Cycles were repeated every 28 days. In the second cycle, the sequence was reversed, so that the patient served as his or her own control regarding sequence-related toxicity. The extent of leukopenia was schedule-dependent, with significantly less toxicity occurring when gemcitabine was administered before the cisplatin. Interestingly, of the five patients with esophageal cancer, one patient achieved a complete response, and two patients achieved a partial response. The mean duration of response for these patients was six months.

In our study, half of the patients required a reduction in the dose of gemcitabine, primarily because of neutropenia. However, since no patients developed neutropenic fever or required hospitalization, in retrospect we think that the dose-reduction guidelines could have been less stringent (20% reduction instead of 50%). In this way, a higher overall dose of the gemcitabine could have been delivered. Secondly, the starting dose of cisplatin should have been lower (perhaps 60 or 75 mg/m^2 instead of 100 mg/m^2) since most of the toxicities that caused patients to be removed from the study were related to the cisplatin rather than to the gemcitabine (nausea, vomiting, ototoxicity, and nephrotoxicity.) One of the deaths was definitely related to the cisplatin, and another one was possibly related. Eight patients discontinued treatment due to toxicity, and perhaps this could have been avoided with a lower dose of cisplatin. Some of the patients had been pretreated with cisplatin or radiation before entry into the study, and they may have been able to better tolerate a more "palliative" regimen with less cisplatin, and yet possibly more gemcitabine.

In this trial, we defined the primary survival endpoint in terms of 3-month survival, since our previous trial for patients with metastatic esophageal cancer and similar eligibility criteria yielded only 3-month median survival. We determined a priori that the regimen would be of further interest if the data were consistent with a true 3-month survival probability of 70% or greater. Eighty-one percent of patients survived 3 months, with median survival of 7 months.

The combination of gemcitabine and cisplatin was quite tolerable, and some of the toxicity could most likely be eliminated with a slight reduction of the cisplatin dose. Median survival was favorable compared to our last protocol for metastatic disease. Future directions in the Southwest Oncology Group include an ongoing trial of gemcitabine and irinotecan in patients with metastatic disease. Because of gemcitabine's dramatic ability to effect radiation-sensitization, the group is also considering a trial of chemoradiation with gemcitabine for patients with locally unresectable disease.

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