Concurrent Cisplatin, Paclitaxel, and Radiotherapy as Preoperative Treatment for Patients with Locoregional Esophageal Carcinoma

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BACKGROUND. A Phase II trial was conducted at the University of Michigan to determine the efficacy of a preoperative regimen of concurrent cisplatin, paclitaxel, and radiation for patients with locoregional esophageal carcinoma.

METHODS. Sixty-nine patients with esophageal carcinoma were treated with cisplatin 75 mg/m^2 on Day 1, paclitaxel 60 mg/m^2 on Days 1, 8, 15, and 22, and radiation 1.5 Gray (Gy) twice per day on Days 1–5, 8–12, and 15–19, for a total dose of 45 Gy. Transhiatal esophagectomy was performed on approximately Day 50.

RESULTS. The treatment regimen was well tolerated. Only 13% of patients developed Grade 3 or 4 neutropenia and 17% of patients required feeding tubes. Ninety percent of all patients had complete tumor resection at the time of surgery. Nineteen percent of patients achieved a complete histologic response in the resected specimen. The median survival period was 24 months. One-, 2-, and 3-year survival probabilities were 75%, 50%, and 34%, respectively.

CONCLUSIONS. This cisplatin-based preoperative regimen, which contained paclitaxel rather than 5-fluorouracil, was well tolerated. The survival data compared favorably with other previously reported combinations. This regimen is a reasonable preoperative approach for patients with localized esophageal carcinoma. ***Cancer*** **2003;98:2177–83.** *© 2003 American Cancer Society.*

KEYWORDS: esophageal carcinoma, chemotherapy, radiation, cisplatin, paclitaxel.

Patients with localized esophageal carcinoma are treated with surgery alone, primary chemoradiation, or chemoradiation followed by surgery. Despite many randomized trials, there is no definitive proof that any one approach is superior. At the University of Michigan (Ann Arbor, MI), we have had an interest for many years in exploring new chemoradiation combinations before surgery. Many chemoradiation regimens have utilized cisplatin and 5-fluorouracil (5-FU), but other agents such as paclitaxel and more recently irinotecan have demonstrated activity in this disease.[1] At the time we designed this study, we decided to further evaluate the role of paclitaxel in a chemoradiation regimen. Ajani et al.[2] reported a Phase II trial in which 46 patients with esophageal carcinoma were treated every 21 days with paclitaxel 250 mg/m^2 and granulocyte–colony-stimulating factor (G-CSF). The partial response rate in their study was 31%. Choy et al.[3] conducted a Phase I trial of concurrent weekly paclitaxel and radiotherapy for patients with nonsmall cell lung carcinoma. Although the trial was not designed for patients with esophageal carcinoma, the radiation fields in patients with lung carcinoma and esophageal carcinoma often include similar anatomic structures. Therefore, the toxicity data were considered relevant to esophageal carcinoma.

When administered along with 60 Gray (Gy) of radiation, paclitaxel 60 mg/m^2 per week was the maximum tolerated dose in that study and esophagitis was the most common dose-limiting toxicity. We designed a trial to combine cisplatin and paclitaxel administered concurrently with radiotherapy, before transhiatial esophagectomy, to determine the efficacy of this combination.

MATERIALS AND METHODS

Eligibility criteria included the following: 1) new diagnosis of histologically confirmed squamous cell carcinoma, adenocarcinoma, or undifferentiatied carcinoma of the esophagus or gastroesophageal junction; 2) no previous treatment; 3) disease limited to the esophagus or regional lymph nodes and able to be encompassed in a single radiation field; 4) no medical contraindication to surgery; 5) a Karnofsky performance status greater than 60%; 6) age younger than 75 years; 7) creatinine clearance greater than 60 mL/min; 8) a white blood cell count greater than 3500 cells per microliter and a platelet count greater than100,000 cells per microliter; 9) no previous malignancy or previous malignancy only if the patient was considered to be cured; 10) no serious medical conditions that would preclude safe administration of treatment; and 11) ability to give informed consent.

Staging

Patients were staged with upper endoscopy and biopsy, barium swallow, and a computed tomograpy (CT) scan of the chest and abdomen. The rare patient with involvement of celiac lymph nodes was not excluded. During this period of time at the University of Michigan, we were not routinely using endoscopic ultrasound or laparoscopy for preoperative evaluation.

Chemotherapy

Paclitaxel 60 mg/m^2 was administered on Days 1, 8, 15, and 22. The drug was diluted in at least 500 mL of 5% dextrose solution or 0.9% sodium chloride solution and infused over 3 hours. All patients were premedicated with dexamethasone 20 mg orally 12 and 6 hours before paclitaxel administration and with diphenhydramine 50 mg intravenously (i.v.) and cimetidine 300 mg i.v. 30 minutes before they received paclitaxel. Vital signs were monitored closely during the infusion.

Cisplatin 75 mg/m^2 was given on Day 1 as a 2-hour infusion. Patients were prehydrated with 1 L of 5% dextrose in 0.9% sodium chloride solution. A 12.5 g mannitol i.v. bolus was given immediately before cisplatin, after which 25 g mannitol in 1000 mL of D5-normal saline was infused over 4 hours during and after the cisplatin infusion. Fluid intake and output were measured carefully and additional fluids were given i.v. to match excessive loss from emesis, diarrhea, or urine.

G-CSF was administered in a dose of 5 μg/kg per day subcutaneously, starting 24 hours after the cessation of the fourth dose of paclitaxel and continuing until the absolute neutrophil count was greater than 10,000 cells per microliter.

Radiotherapy

All patients were positioned supine in a customized low-density foam cradle and underwent a treatment planning CT scan in the same position. Within our three-dimensional conformal treatment planning system, a gross tumor volume (GTV) was identified based on abnormalities observed in the esophagus, proximal stomach, and regional lymph nodes on a pretreatment diagnostic CT scan and barium swallow and at the time of esophagus copy (EGD). A planning target volume (PTV) then was identified by expanding the GTV 5 cm superiorly and inferiorly and 1.5 cm radially. Steps were taken to ensure that all enlarged lymph nodes were adequately covered by the PTV. Uninvolved lymph node regions were not purposefully included. The goals of treatment planning were to encompass the PTV with the 95% isodose surface and to minimize the dose to the surrounding normal structures. The dose to the spinal cord was limited to 36 Gy in all cases. A four-field conformal beam arrangement consisting of opposed anterior and posterior and lateral fields typically was used. A dose of 1.5 Gy was delivered twice daily on Days 1–5, 8–12, and 15–19 with a minimum interfraction interval of 6 hours, resulting in a total dose of 45 Gy.

Preoperative Assessment

Patients underwent a repeat CT scan of the chest and abdomen and barium swallow approximately 1 week before the planned esophagectomy to rule out development of metastatic disease that would preclude surgery.

Surgery

Transhiatal esophagectomy was performed on approximately Day 50. Through an upper midline abdominal incision and a cervical incision, the entire thoracic esophagus was mobilized and resected from the level of the clavicles to the gastric cardia. The remaining stomach was mobilized and positioned in the posterior mediastinum in the original esophageal bed. Alimentary continuity was reestablished by anastomosis between the cervical esophagus and the gas-

tric fundus, above the level of the clavicles. A gastric drainage procedure, generally a pyloromyotomy, and a feeding jejunostomy were performed routinely. In patients with previous gastric surgery and an inadequate remaining length of stomach to reach to the neck for a cervical esophageal anastomosis, the esophagus was replaced with colon. Accessible intraabdominal, paraesophageal, and subcarinal lymph nodes were sampled for the purpose of staging.

Statistical Design

The primary objective was to determine the rate of complete histologic response induced by the preoperative regimen of chemoradiation. A second objective was to determine the overall survival and time to disease recurrence in patients treated with this regimen.

In a former trial at the University of Michigan, 25% of patients treated with a fairly toxic preoperative regimen of cisplatin, 5-FU, vinblastine, and radiation achieved a complete response.[3] Our goal was to demonstrate that if the new regimen could be equivalent in efficacy to the previous regimen, it could be considered superior because paclitaxel is generally less toxic than 5-FU and vinblastine. We would consider the paclitaxel preoperative regimen to be equivalent to the vinblastine regimen if the 1-sided lower bound of the 95% confidence interval (CI) for a histologic complete response (CR) included 0.20. The 1-sided lower bound of the 95% CI for an observed rate of 32.5% is 20.4%.

RESULTS

Patient Characteristics

Between January 1995 and September 1997, 69 patients were enrolled in the current study. Written informed consent was obtained from all patients. Patient characteristics are summarized in Table 1. The majority of patients were male and a preponderance had adenocarcinoma.

TABLE 1
Patient Characteristics

Characteristic	No. (%)
No. of patients	69
Gender	
Male	62 (90)
Female	7 (10)
Age (yrs)	
Mean	60
Range	33–71
Histology	
Adenocarcinoma	57[a] (83)
Squamous cell carcinoma	10 (14)
Undifferentiated	2 (3)
Lymphadenopathy on CT	
Yes	33 (48)
No	36 (52)

CT: Computed tomography.
[a] Includes 20 cases of Barrett esophagus.

Toxicity

Treatment was generally very well tolerated. One patient had an allergic reaction to paclitaxel during the first few minutes of his first infusion, which consisted of flushing, dyspnea, tachycardia, and chest tightness. He recovered without sequelae and was treated with two cycles of cisplatin and 5-FU concurrent with the radiation. The remaining 68 patients received the full dose of cisplatin as planned and 50 patients (72%) received 100% of the planned dose of paclitaxel. Twelve patients (17%) required feeding tube support. There were no preordained criteria for feeding tube placement, but decisions were based on the patient's ability to maintain adequate hydration and nutrition. Grade 3/4 neutropenia was experienced by 9 patients (13%). Three patients (4%) experienced febrile neutropenia. Two patients (3%) required a blood transfusion for anemia.

Surgery Results

Sixty-eight patients underwent surgery. The one patient who did not undergo resection experienced total esophageal obstruction during preoperative treatment. During endoscopy to attempt dilatation and laser treatment, a perforation of the esophagus occurred. He subsequently underwent stent placement and completed definitive radiation without surgery.

Sixty-one patients (90 %) had no macroscopic residual tumor, and 7 patients (10 %) had metastatic disease. There was one intraoperative death. Thirteen patients (19%) achieved a histologic CR.

Survival

All 69 patients were included in the survival analysis. The survival probability estimates were obtained by the Kaplan–Meier method. The median follow-up time was 24 months for all patients and 47 months for patients who still were alive. Forty-nine patients (71%) died of disease or other causes. The median survival time was 24 months (95% CI, 16–33). The 1-, 2-, and 3-year survival probabilities were 75% (95% CI, 65–86%), 50% (95% CI, 39–63%), and 34% (95% CI, 23–46%), respectively. The Kaplan–Meier curve for overall survival is shown in Figure 1.

The effects of some variables (age, histology, Barrett esophagus, lymphadenopathy on CT scan, T clas-

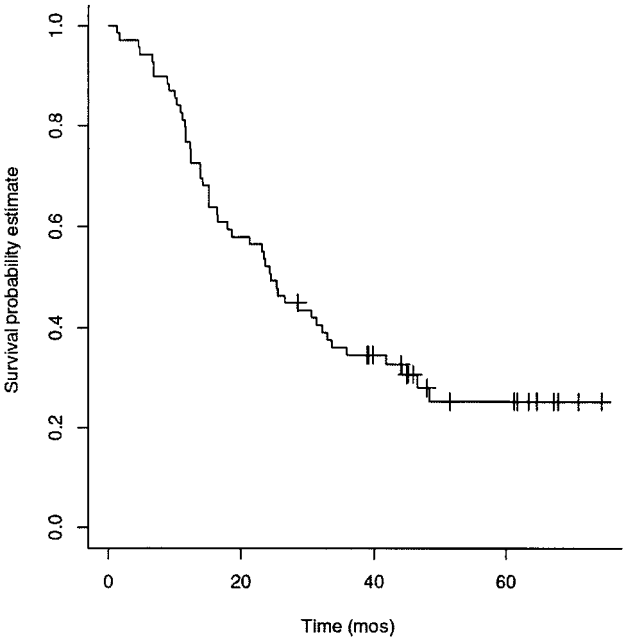

FIGURE 1. Overall survival.

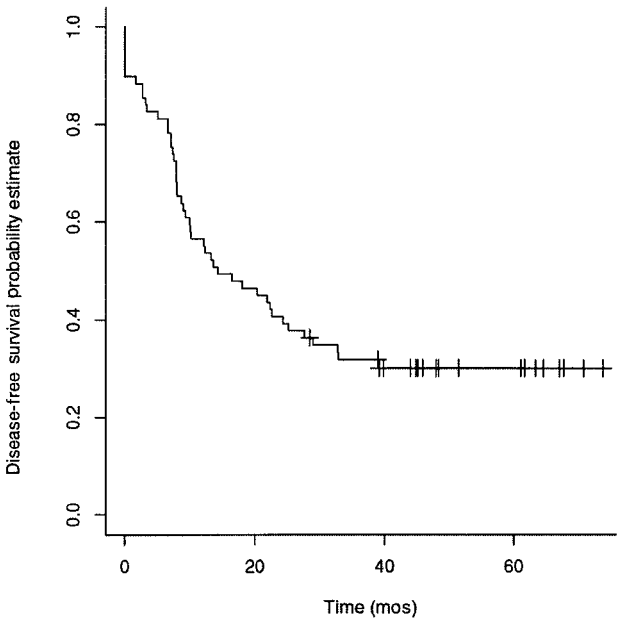

FIGURE 2. Disease-free survival.

TABLE 2
Risk Ratios for Overall Survival

Variable	No.	RR	95%	CI	*P* value
Age					
Younger than median	35	1.0	—	—	—
Older than median	34	1.0	0.6	1.8	0.91
Histology					
Adenocarcinoma	57	1.0	—	—	—
Squamous cell carcinoma	10	0.3	0.1	1.0	0.05
Barrett esophagus					
No	37	1.0	—	—	—
Yes	20	0.6	0.3	1.1	0.13
Lymphadenopathy on CT					
No	36	1.0	—	—	—
Yes	33	1.4	0.8	2.5	0.22
T classification					
T_0	16	1.0	—	—	—
T1–T2	21	2.1	0.9	5.2	0.10
T3–T4	25	2.5	1.0	5.9	0.04
N classification					
N_0	28	1.0	—	—	—
N1	31	1.7	0.9	3.3	0.09

RR: risk ratio; CI: confidence interval; CT: computed tomography.

sification, and N classification) on survival and the corresponding risk ratios were determined based on Cox proportional hazard models (Table 2). A marginally significant effect was found only for histology ($P = 0.05$), in favor of squamous cell carcinoma (risk ratio, 0.3) compared with adenocarcinoma. Not surprisingly, the risk ratios indicate that a higher T classification and a higher N classification are associated with an adverse effect on patient survival. Compared with T0 tumors, the risk ratio for T1–T2 tumors was 2.1 and the risk ratio for T3–T4 tumors was 2.5. The risk ratio for N1 disease was 1.7 compared with N0 disease.

Disease-free survival probability was investigated using the Kaplan–Meier method and was measured from the start of treatment until disease recurrence. Of the 69 patients, 8 patients (12%) were never rendered free of disease and therefore were considered to have no disease-free time. This included one patient who died during surgery and one patient who withdrew from the study. Forty patients (58%) eventually had a recurrence of disease. The median disease-free survival time was 14 months (95% CI, 9–25). The 1-, 2-, and 3-year disease-free survival probabilities were 55% (95% CI, 43–67%), 39% (95% CI, 28–51%), and 32% (95% CI, 21–43%), respectively. The disease-free survival curve is shown in Figure 2.

Landmark Analysis: Complete Responders Versus Non–Complete Responders

Overall and disease-free survival times were compared between complete responders (those with T0N0 at surgery) and nonresponders. To avoid potential biases, landmark analysis was performed.[4] The landmark time by which all patients' responses were determined was set at 3 months after the start of treatment. Only patients with survival times longer than 3 months were included in the current analysis.

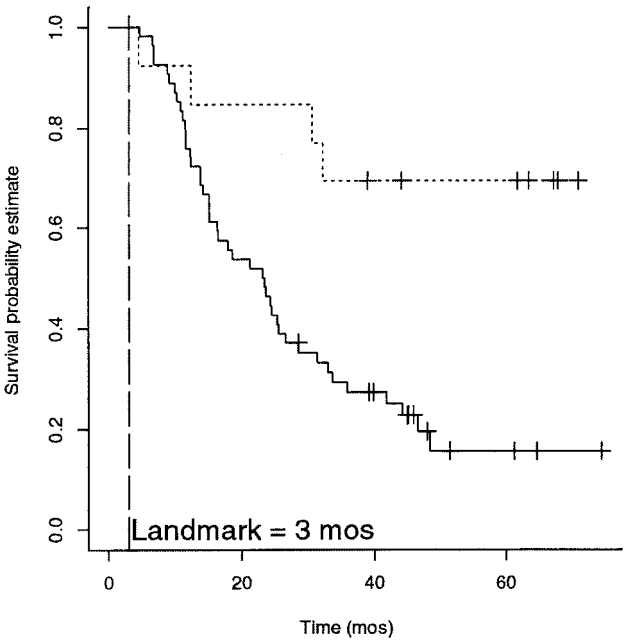

FIGURE 3. Overall survival for complete responders and non-complete responders. Solid line: non-complete responders; dotted line: complete responders.

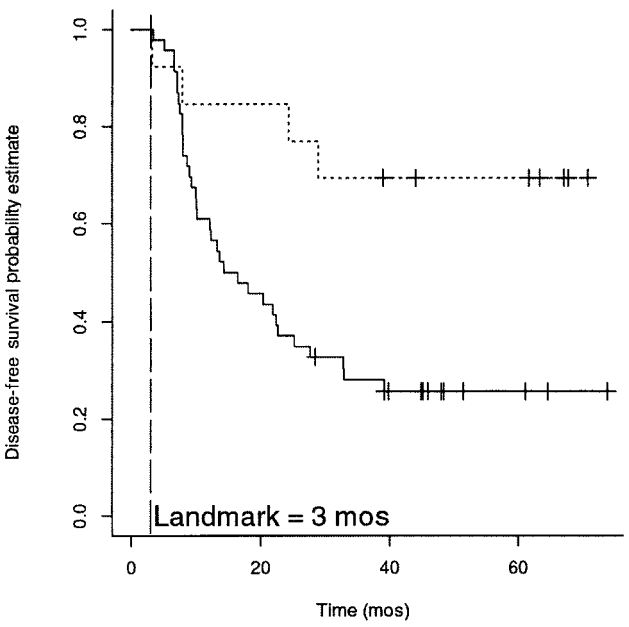

FIGURE 4. Disease-free survival for complete responders and non-complete responders. Solid line: non-complete responders; dotted line: complete responders.

Survival probability estimates were obtained using the Kaplan–Meier method.

Landmark Survival

Sixty-seven patients who were known to have survived beyond the 3-month landmark time were included in the current analysis. Of these 67 patients, 13 (22%) were complete responders. Figure 3 shows the Kaplan–Meier curves for complete responders and nonresponders. The 1-, 2-, and 3-year survival probabilities for the complete responders were 85% (95% CI, 65–100%), 85% (95% CI, 65–100%), and 69% (95% CI, 44–94%), respectively. The 1-, 2-, and 3-year survival probabilities for the nonresponders were 74% (95% CI, 62–86%), 44% (95% CI, 31–58%), and 27% (95% CI, 15–39%), respectively.

Fifty-nine patients who had at least 3 months of disease-free survival time were included in the current analysis. Of these 59 patients, 13 (22%) were complete responders. Figure 4 shows the Kaplan–Meier curves for complete responders and nonresponders. The 1-, 2-, and 3-year disease-free survival probabilities for the responders were 85% (95% CI, 65–100%), 77% (95% CI, 54–100%), and 69% (95% CI, 44–94%), respectively. The 1-, 2-, and 3-year survival probabilities for the nonresponders were 59% (95% CI, 44–73%), 37% (95% CI, 23–51%), and 28% (95% CI, 15–41%), respectively.

DISCUSSION

Patients treated with cisplatin, paclitaxel, and concurrent radiation in the current trial tolerated the regimen well. Only 13% of patients experienced Grade 3 or 4 neutropenia and 17% required feeding tubes. We were disappointed that the histologic CR rate was only 19%. Yet, the median survival period was 24 months and the 1- and 3-year survival rates were 75% and 34%, respectively. This compares favorably with other trials of preoperative chemoradiation for esophageal carcinoma. Urba et al.[5] published a randomized trial of preoperative chemoradiation versus surgery alone performed at the University of Michigan. The chemotherapy regimen, which was substantially more intensive, comprised a cisplatin total dose of 200 mg/m^2, 5-FU, and vinblastine. The associated toxicity was greater: the rate of Grade 3 or 4 granulocytopenia was 78%, and 63% of patients required feeding tubes. However, in that study, the median survival period for patients who received the multimodality treatment arm was 17 months, which is poorer than the median survival period achieved in the current study. The 1- and 3-year survival rates for the multimodality arm in the randomized trial were 72% and 30%, respectively, which are extremely similar to the rates in the current study. We have not become more selective in evaluating patients for the trials. All patients in both trials were staged in a similar fashion, and unless there was evidence of metastatic disease or a true contraindica-

tion to subjecting a patient to this type of therapy, all patients were offered the protocol treatment.

Several other trials have been conducted to evaluate preoperative chemoradiation before surgery. Walsh et al.[6] reported on 58 patients with adenocarcinoma who were treated with cisplatin, 5-FU, and radiation before surgery versus 55 patients treated with surgery alone. The survival rates for the multimodality group were 52% at 1 year and 32 % at 3 years. The trial conducted by Walsh et al. is the only one that has shown statisticial superiority for the chemoradiation arm, but the surgical arm survival rate of 6% at 3 years is inferior to the results typically achieved with surgery alone. Bossett et al.[7] reported the results of a randomized trial conducted by the European Organization for Research and Treatment of Cancer, in which 282 patients with Stage I and II squamous cell carcinoma of the esophagus were treated with either preoperative cisplatin and radiation or surgery alone. The multimodality group achieved a 1-year survival rate of 72% and a 3-year survival rate of 36%. Recently, Burmeister et al.[8] reported the results of a large Australian trial comparing surgery alone with preoperative cisplatin, 5-FU, and radiation in 256 patients with esophageal carcinoma. The median survival was similar for both arms. For the chemoradiation arm, the 1-year survival rate was 75% and the 3-year survival rate was 35%. These rates are quite similar to the rates achieved in the current trial.

Historically, most trials have shown evidence that histologic complete responders have better survival than patients with evidence of residual disease at time of surgery. This also is true in the current study, as reflected in Figure 3. Although 81% of patients had residual tumor in their esophagus after the preoperative treatment with chemoradiation, the 1- and 3-year survival rates for this "poorer prognosis" group were very good (i.e., 74% and 27%, respectively), resulting in a reasonable survival rate for the whole group. We believe that these results strongly support to the role of surgery as part of the treatment regimen for these patients. Surgery can eliminate the disease that persists after chemoradiation, allowing 27% of patients in the current study to be alive at the 3-year follow-up.

Paclitaxel was introduced recently to preoperative regimens to determine whether this agent can increase efficacy or whether it can serve as an appropriate substitute for 5-FU, which has the fairly troubling side effects of mucositis and diarrhea. Paclitaxel and radiation have been combined because paclitaxel synchronizes cells at G2/M, a relatively radiosensitive phase of the cell cycle. In one Phase I study, the maximum tolerated dose of paclitaxel was 50 mg/m^2 per week for 6 weeks with once-daily radiation to a total dose of 50 Gy.[9] The dose-limiting toxicities were pain within the radiation field, nausea, and anorexia.

In another trial, paclitaxel and cisplatin were given concurrently with radiation to 41 patients with esophageal carcinoma.[10] The paclitaxel dose was 60 mg/m^2, and the cisplatin dose was 25 mg/m^2; both were administered weekly for 4 weeks, with once-daily radiation to a total dose of 39.6 Gy in 1.8 Gy fractions. Only 5% of patients had Grade 4 esophagitis requiring parenteral nutrition. Twenty-nine percent of patients achieved a CR and a 2-year survival rate of 42%. The 2-year survival rate of 50% reported in the current study compares favorably with that trial. Adelstein et al.[11] reported their experience with 2 cycles of cisplatin 20 mg/m^2 per day for 4 days and paclitaxel 175 mg/m^2 for 1 day concurrent with a split course of accelerated radiation (1.5 Gy twice per day to a total dose of 45 Gy with a 12-day break). Forty patients with locally advanced esophageal carcinoma were treated, and 93% had disease that was resectable for cure, with a 3-year survival rate of 30%. There was no survival advantage and more toxicity when compared with historical control patients treated with a cisplatin and 5-FU–based combination. However, the radiation was accelerated and the paclitaxel was delivered in monthly high doses, rather than in weekly low doses.

Paclitaxel has also been added to the classic regimen of cisplatin, 5-FU, and radiation for patients with esophageal carcinoma. Investigators at The University of Texas M. D. Anderson Cancer Center reported a trial involving 2 courses of induction chemotherapy with cisplatin, 5-FU, and paclitaxel before 45 Gy of radiation in 1.8 Gy fractions that was delivered concurrently with a course of cisplatin and 5-FU.[12] The regimen resulted in a 30% histologic CR. The median follow-up was only 20 months, but the 1-year survival rate was 81%.

Heath et al.[13] conducted a Phase II trial of continuous-infusion cisplatin and 5-FU with radiotherapy, followed by esophagectomy and then three postoperative cycles of cisplatin and paclitaxel. Forty-two patients were enrolled, 39 of whom proceeded to surgery. They achieved a 26% pathologic CR rate. At a median follow-up of 30.2 months, the median survival time was not yet reached and the 2-year survival rate was 62%.

The current trial supports the feasibility of incorporating paclitaxel into perioperative regimens for patients with esophageal carcinoma. The toxicity profile is different from 5-FU and may be better tolerated in some patients. However, because recurrent disease is not uncommon after chemoradiation followed by surgery, future directions include incorporating newer agents into chemotherapy combinations and attempt-

ing to control residual micrometastatic disease with antiangiogenic agents or other unique targeted therapy. The role of preoperative chemoradiation and surgery may be maximal debulking of the tumor, followed by long-term treatment with targeted therapy intended to prevent the growth of microscopic disease. Our future direction at the University of Michigan includes preoperative chemoradiation followed by chronic suppressive therapy with an antiangiogenic agent.

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