Preoperative chemotherapy for esophageal cancer with paclitaxel and carboplatin: Results of a phase II trial

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Objective: Paclitaxel has one of the highest response rates when used as a single agent in patients with esophageal cancer. The combination of paclitaxel and carboplatin has been shown to be a well-tolerated and safe regimen in non-small cell lung cancer. The objective of this study was to determine the efficacy of preoperative paclitaxel and carboplatin in patients with carcinoma of the esophagus.

Patients and Methods: A phase II trial was initiated in January 1999 and concluded in January 2001. All patients had potentially resectable disease (including clinical T4 lesions). Patients with stage I disease and those with visceral metastases were excluded. All underwent preoperative computed tomography scanning and endosonography for staging. Paclitaxel (200 mg/m²) and carboplatin (area under the curve = 6) were given on days 1 and 22. Esophagectomy was carried out on weeks 6 to 8.

Results: Twenty-six (11 epidermoid, 15 adenocarcinoma) patients completed the trial. Median age was 61.5 and 85% were men. Preoperative staging showed: stage IIA, 6 patients; stage IIB, 1 patient; and stage III, 19 patients. All patients completed their preoperative chemotherapy. There was no unexpected chemotherapy-related toxicity. A major clinical response was achieved in 16 patients (61%: 19% complete, 42% partial). Resectability was 77% (20/26). A complete pathologic response was seen in 11% of all patients and in 25% of those with epidermoid cancer. Hospital mortality and morbidity were 4 and 27%, respectively. Overall 3-year survival was 48% (64% for resected patients, median not reached). All 6 unresectable patients died within 6 months of exploration.

Conclusion: Paclitaxel-carboplatin combination is a safe and well-tolerated regimen for esophageal cancer with clinical response rates comparable to historical controls. This regimen may be especially suitable for patients with epidermoid cancer, who had a 25% pathological complete response in this report.

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Supported by a grant from Bristol-Myers Squibb.

Presented at the 38th Annual Meeting of the American Society of Clinical Oncology, Orlando, Fla, May 18-21, 2002.

Received for publication Nov 11, 2002; revisions requested Feb 5, 2003; revisions received April 11, 2003; accepted for publication April 21, 2003.

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J Thorac Cardiovasc Surg 2003;126:1603-8

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0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(03)00710-4

Although esophagectomy remains the standard of care for esophageal cancer, the reported survival following conventional resection techniques rarely exceeds 30%.¹⁻⁸ We have previously reported our results after radical en bloc esophagectomy.⁹ The 5-year overall and disease-free survival was 46 and 40%, respectively. Importantly, locoregional recurrence (defined as anastomotic recurrence or any recurrence within the operative field) occurred in fewer than 10% of patients. This low local failure rate compares favorably with that reported after chemoradiation alone¹⁰ or that following preoperative chemoradiation.¹¹ Therefore, we have elected not to include radiotherapy in our treatment strategies for esophageal cancer. However, because more than 50% of patients eventually die due to systemic disease, a reasonable argument could be made for including chemo-

therapy in any treatment paradigm for this disease. Several randomized trials have evaluated the merit of preoperative chemotherapy compared with surgery alone.²⁻⁵ The chemotherapy regimen of choice in most trials of preoperative chemotherapy was cisplatin and 5-fluorouracil. This regimen generally results in a clinical response rate of 50% to 70% and a complete pathological response in less than 5% of patients.^{2,4}

The microtubule interfering agent paclitaxel has demonstrated significant activity in esophageal carcinoma, with a 32% response rate in patients with metastatic or locally advanced disease.^{12,13} Carboplatin, an analog of cisplatin, has activity similar to cisplatin in a number of tumor types, and it provides several practical advantages over cisplatin. First, nausea and vomiting related to carboplatin are substantially less than with cisplatin, which may be an advantage in a population that is already nutritionally compromised. Second, the relative lack of nephrotoxicity and decreased need for hydration allows treatment in the outpatient setting and decreases the likelihood of dose reductions or delays due to nephrotoxicity. Finally, the combination of paclitaxel and carboplatin has been extensively studied in a variety of tumor types, and its toxicities are well established and generally considered to be quite tolerable. For these reasons, and encouraged by the ability of en bloc resection to improve local disease control, we elected to examine the efficacy of the combination of paclitaxel and carboplatin given prior to en bloc esophagectomy.

Patients and Methods

From January 1999 to May 2001, 26 patients with histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus were entered into this study. Patients were considered eligible if they had disease limited to the esophagus and regional lymph nodes. Preoperative evaluation included a complete history and physical examination, routine laboratory evaluation, esophagogastroduodenoscopy, endoscopic ultrasonography (EUS), barium swallow, and computed tomography (CT) scan of the chest and upper abdomen. Patients were excluded if they had intramucosal or submucosal tumors as determined by preoperative EUS. Patients were also considered ineligible for the study if they received prior chemotherapy or radiotherapy, had unstable cardiovascular disease, had a Karnofsky performance status of <70%, or had inadequate pulmonary, renal, hepatic, or hematologic function to undergo chemotherapy and the subsequent planned operation. The study design was reviewed and approved by the institutional review board, and informed consent was obtained from all patients.

Treatment Plan

All patients received 2 cycles of paclitaxel and carboplatin 21 days apart. Paclitaxel 200 mg/m² was given as a 3-hour infusion, followed by carboplatin dosed to an area under the curve of 6 by the Calvert formula, given as a 1-hour infusion. All patients were premedicated with dexamethasone 20 mg by mouth, given approx-

imately 7 and 12 hours before each dose of chemotherapy, and with granisetron 0.7 mg intravenous (IV), dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and famotidine 20 mg IV, given immediately before each dose of chemotherapy. Restaging evaluation was carried out 2 to 3 weeks after the second cycle of chemotherapy. Restaging included a CT scan of the chest and upper abdomen and esophagogastroduodenoscopy. All patients without evidence of systemic disease on posttreatment staging underwent surgical exploration 6 to 8 weeks after the first course of preoperative chemotherapy.

Response

A clinical complete response was defined as complete absence of tumor on the CT scan and the absence of tumor on endoscopic biopsy. A partial response was defined as a 50% reduction in tumor length as determined by posttreatment contrast esophagogram or esophagoscopy. A complete pathological response was defined as the absence of any tumor in the esophagus and resected lymph nodes.

Surgical Resection

All patients had an en bloc esophagectomy as previously described.¹⁴ Briefly, the tumor-bearing esophagus was resected en bloc within a wide envelope of adjacent tissues including both pleural surfaces laterally, the pericardium anteriorly, and all lymphatic and areolar tissues wedged dorsally between the esophagus and the spine. Additionally, the thoracic duct was resected en bloc with the esophagus and a complete mediastinal and upper abdominal lymphadenectomy was performed. Neither the azygous trunk nor the intercostal vessels were included in the resection. Fifteen patients also underwent dissection of the lymph nodes in the superior mediastinum along both recurrent laryngeal nerves, as well as a modified infraomohyoid cervical lymph node dissection as previously described.¹⁵

Postoperative Therapy

Patients who had an objective clinical response or those with stable disease received 2 postoperative cycles of the same preoperative chemotherapy. No adjuvant radiotherapy was planned. Postoperative treatment of incompletely resected patients or those with unresectable or progressive disease was left to the discretion of the treating physician.

Follow-up

Follow-up was complete in all patients until death or December 2002. Patients were seen in the thoracic oncology clinic every 3 months. Follow-up evaluation included physical examination, routine laboratory analysis, and chest radiography at each visit. A CT scan of the chest and upper abdomen was performed at 6 months and 12 months postoperatively, then yearly thereafter. Recurrence was documented histologically in all cases. The median follow-up was 22 months for all patients and 27 months for resected patients.

Statistics

Kaplan-Meier survival analysis was performed to estimate the overall survival probabilities for all patients and separately for resected patients. Ninety-five percent confidence intervals for all

TABLE 1. Patient characteristics

Age range	36–77
Median age	61.5
Male/female	22/4
Race	
White	20 (77%)
Asian	2 (8%)
Hispanic	4 (15%)
Cell type	
Adenocarcinoma	15 (58%)
Squamous	11 (42%)
TNM stage	
T3 N0	6
T2 N1	1
T3 N1	14
T4 Nx	2
T4 N1	3

TABLE 2. Preoperative chemotherapy toxicities (grades 3 to 4)

Toxicity	Patients
Leukopenia	6 (12%)
Anemia	3 (6%)
Thrombocytopenia	1 (2%)
Myalgia/arthritis	1 (2%)
Nausea/vomiting	0
Neuropathy	0
Neutropenic fever	2 (4%)

estimated survival probabilities were calculated to assess the precision of the estimates.

Results

Twenty-six patients were enrolled between January 1999 and January 2001. Patient characteristics are shown in Table 1. Median age was 61.5 years, and the majority of patients were men (85%). Eleven patients (42%) had squamous cell carcinoma and 15 (58%) had adenocarcinoma. Pretreatment clinical stages were as follows: stage IIA, 6 patients (27%); stage IIB, 1 patient (8%); stage III, 19 patients (65%).

Induction Therapy

All 26 patients completed both cycles of paclitaxel and carboplatin preoperatively. One patient required dose reduction due to neutropenia with fever, but subsequently developed neutropenic fever after the second course of treatment at a reduced dose. Grade 3 to 4 granulocytopenia occurred in 6 cycles of chemotherapy (12%). Other toxicities, listed in Table 2, were generally mild and easily treated.

Response to Therapy

Twenty-five of 26 patients (95%) reported a subjective improvement in dysphagia within 1 week after the first course of chemotherapy. Eleven patients (42%) had a partial

TABLE 3. Postoperative complications

Mortality (sepsis)	1 (4%)
Morbidity	
Arrhythmia	4 (16%)
Anastomotic leak	2 (8%)
Respiratory failure	3 (12%)
Wound infection	1 (4%)
Pulmonary embolus	1 (4%)
Laryngeal nerve injury	1 (4%)
Gastrotracheal fistula	1 (4%)
Total	13 (7 patients, 28%)

TABLE 4. Treatment results

Pretreatment stage	Posttreatment stage
T0 N0: 0	T0 N0: 3 (12%)
I: 0	I: 0
IIA: 6 (23%)	IIA: 6 (23%)
IIB: 1 (3.8%)	IIB: 1 (4%)
III: 19 (73%)	III: 8 (31%)
IV: 0	IV: 7 (27%)

clinical response to chemotherapy and 5 (19%) had a complete clinical response, as previously defined. One patient had clinical progression of disease.

Surgical Treatment

One patient had disease progression as evidenced by liver metastases detected on restaging CT scan and was taken off study. Twenty-five patients underwent surgical exploration. Surgical mortality and morbidity were 4 and 28%, respectively (Table 3). Five patients with clinical T4 disease were unresectable at thoracotomy due to direct airway invasion (n = 3) or aortic invasion (n = 2). Esophagectomy was carried out in 20 patients. Fifteen patients whose tumors were located within the tubular esophagus underwent 3-field lymph-node dissection, and 5 patients with tumors involving only the gastroesophageal junction underwent 2-field lymph-node dissection. Eighteen patients had an R-O resection (69%); 1 patient had an R-1 resection (microscopic residual disease at the esophageal margin); and 1 patient had an R-2 resection due to intraoperatively detected previously unsuspected liver metastases. Seven of 15 patients who had a 3-field lymph node dissection were found to have occult previously unsuspected metastases to the recurrent laryngeal lymph nodes, including the previously mentioned patient who also had unsuspected liver metastases. Three of 20 patients (11%) had a complete pathological response and all had squamous histology. No patient with adenocarcinoma had a complete pathologic response. Overall, 7 patients were down-staged and 10 were up-staged including 6 patients found to have M_{1a} disease based on recurrent laryngeal nodal metastases (Table 4).

Figure 1. Kaplan-Meier survival for all patients.

Survival

Overall actuarial 3-year survival was 48% (95% confidence interval; 27%-68%) for all 26 patients based on an intention-to-treat analysis (Figure 1). All 5 patients with unresectable disease died within 6 months of surgical exploration. Overall actuarial 3-year survival for the 20 resected patients was 64% (95% confidence interval, 39%-85%; median not reached; Figure 2). Three of the 7 patients with positive recurrent laryngeal nodes are alive; 1 has recurrent disease and 2 are disease-free.

Discussion

Though the potential benefits of preoperative chemotherapy have been studied extensively, there has been no clear demonstration of a survival benefit associated with that approach, with the possible exception of those patients who achieve a complete pathologic response.^{3,5} Unfortunately, complete pathological response rates after the commonly used regimen of 5-fluorouracil and cisplatin is only 3%.² The addition of preoperative radiation to chemotherapy results in higher response rates; however, a survival benefit has not been demonstrated in most of the published randomized trials that compared trimodality therapy with surgery alone.⁶⁻⁸ Furthermore, the high local failure rate after chemoradiation alone (34%) or after induction chemotherapy (39%) argues against regimens that add radiation to chemotherapy and surgery. In contrast, the use of

preoperative chemotherapy may be ideally suited for the treatment of a disease where more than 50% of relapse occurs at distant sites.

The introduction of newer, more active chemotherapeutic agents with improved therapeutic index invites further evaluation of this treatment strategy. In particular, paclitaxel has demonstrated high efficacy in esophageal cancer^{12,13} and, because of its favorable toxicity profile and synergy with platinum derivatives, appears well suited for study in the preoperative setting. Because pathologic complete response seems to correlate with survival benefit, an improvement in these parameters in a pilot trial would warrant further investigation in a larger controlled trial.

In this trial we investigated the feasibility and efficacy of taxane-based chemotherapy given alone before esophagectomy. The data suggest the regimen is feasible and safe, with a 4% treatment-related mortality. All but 1 patient completed the preoperative therapy at the prescribed dose. Chemotherapy-related complications were generally well tolerated. The overall clinical response rate was 61% and was comparable to that reported with other regimens. The response rates reported herein are of particular interest as patients with stage I disease were specifically excluded from the study and 5 patients with clinical T-4 disease were included, thus biasing the study population toward more advanced stages. Nonetheless, relief of dysphagia was

Figure 2. Kaplan-Meier survival for patients undergoing resection.

promptly achieved in over 90% of patients, obviating the need for parenteral or enteral nutritional support during chemotherapy. The R-0 resection rate reported in this trial is only 69%. If only patients with potentially resectable disease at enrollment are considered, the R-0 resection rate would approach 90%. The overall resectability rate is based on an intention-to-treat analysis including 6 patients with clinical T-4 disease. One of these patients developed systemic disease after induction chemotherapy, and the remaining 5 patients were found unresectable at thoracotomy either due to aortic ($n = 2$) or major airway invasion ($n = 3$). It is possible that in this subgroup of patients, better response rates may be achievable after preoperative chemoradiation compared with induction chemotherapy alone.

Finally, the complete pathological response rate was 11% for the whole group and 15% for those with resectable disease. The complete pathological response rate was 25% for patients with squamous cell carcinoma and suggests that taxane-based chemotherapy may be particularly useful in this subset of patients.

Despite these encouraging results, the findings in 15 patients who underwent 3-field lymph node dissection are alarming. Nearly 50% of patients had unsuspected nodal metastases to the recurrent laryngeal nodes and in 2 patients that was the only site of nodal disease. Both had squamous cell carcinoma, located in the upper third in the first patient and the lower third in the other. The prevalence of nodal

disease in this potentially resectable group of patients suggests either the need for extending the limit of nodal dissection after conventional esophagectomy or inclusion of these areas in any planned pre- or postoperative radiation port. Nonetheless, among 7 patients with metastases to the recurrent laryngeal nodes, 2 (28%) are alive and free of disease. Although the numbers are small, the 25% to 30% 5-year survival in patients with recurrent laryngeal nodal disease is consistent with our previously reported results.¹⁵

In summary, this pilot trial demonstrates significant activity and tolerable toxicity for the combination of carboplatin and paclitaxel in the preoperative treatment of esophageal cancer, with no impact on surgical morbidity and mortality. These results should be confirmed in a larger phase II trial.

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