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Review paper

Chemotherapy in esophageal cancer

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Esophageal cancer is a virulent malignancy, with the conventional approach of surgery or radiation therapy offering patients only a small chance for long-term disease-free survival. The frequent early systemic dissemination of disease has prompted an ongoing interest in the study of chemotherapy. A broad range of antitumor agents have been studied which demonstrate moderate antitumor activity. A number of combination chemotherapy regimens, mainly cisplatin-based, have been studied, which have consistently greater antitumor activity in local regional disease compared with metastatic disease. The use of preoperative chemotherapy in the surgical treatment of the disease remains investigational. Results from clinical trials comparing radiation therapy alone with concurrent radiation and chemotherapy demonstrate a survival benefit for the use of a combination of concurrent chemotherapy and radiation compared to radiation therapy alone. However, current studies with conventional chemotherapy, radiation and surgery are likely to impart at best a modest to moderate improvement in the treatment of esophageal carcinoma. The priority in chemotherapy trials, therefore, remains the identification of new active chemotherapy agents. The search for novel therapeutic approaches, exploiting advances in understanding of the molecular biology of the disease, continues.

Key words: Cancer, chemotherapy, esophageal.

Introduction

In 1993, 11 300 new cases of esophageal cancer will be diagnosed in the US and 10 200 patients will die of their disease, representing 1.9% of American cancer deaths.[1] An association with abuse of tobacco and alcohol and the development of epidermoid carcinoma of the esophagus is generally accepted.[2] The regional occurrence of esophageal cancer varies dramatically, with a particularly high incidence observed in northern China, the Caspian Littoral and the Transkei province of South Africa.[3–5] The epidemilogic factors responsible for the geographic variability in incidence of esophageal cancer, including potential dietary and environmental carcinogens, remain indeterminate. Adenocarcinoma of the esophagus, which in the past represented only a small proportion of cases of esophageal cancer, is rapidly overtaking epidermoid carcinoma as the predominant disease histology in the US. Indeed, esophageal adenocarcinoma poses a daunting health care problem with cases increasing at an annual rate exceeding that of any other malignancy including malignant melanoma.[6]

The prognosis for patients treated with the standard approach of surgery or radiation therapy alone is dismal. The largest retrospective series of patients treated with either surgery alone or radiotherapy alone, reviewed by Earlam and Cunha-Melo, reported equally poor 2 year survivals of 6–8% and 5 year survivals of 4–6%.[7] The operative mortality for surgically treated patients in this review was a sobering 29%. The significant operative mortality has fueled an ongoing debate regarding the relative efficacy of surgery and radiation therapy, although more recent surgical series from single institutions have reported operative mortalities of 5–15%, with Muller *et al.* reporting a rate of 12.5% in a recent surgical review.[8] Ultimately, the majority of patients treated with either surgery or radiation therapy are destined to die of their disease.

The failure of standard therapy, even in patients with disease clinically limited to the local regional area prior to treatment, is due both to local regional failure and to early systemic dissemination of disease. Western autopsy series and a recent autopsy series from Hong Kong bear out the frequent systemic nature of the disease, even at or shortly after initial presentation.[9–12] Despite the brief duration of illness in these patients, the majority were found at autopsy to have evidence of distant

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metastatic disease whether or not residual local disease was present. The clear need to address early systemic spread of disease with systemic treatment has led to the incorporation of chemotherapy into combined modality therapy employing surgery and radiation therapy. Chemotherapy in the treatment of esophageal carcinoma, both in the palliative setting and in the context of combined modality therapy with curative intent, will be the subject of this review.

Response assessment

Chemotherapeutic agents in esophageal cancer were initially studied in patients with either locally advanced, inoperable disease or distant metastatic disease. Metastatic lesions, including lung or liver metastases, lymph nodes or skin nodules represent measurable disease in which antitumor response to chemotherapy can be readily assessed. The standard objective response criteria, outlined by Miller *et al.*[13], can be easily applied to these lesions: a major response is defined as a greater than 50% reduction in the tumor area calculated by summing the products of the greatest perpendicular tumor diameters. Local regional disease, on the other hand, is evaluable for response by barium esophagram, computed tomography scan or endoscopy, but does not have clearly measurable perpendicular tumor diameters. Relief of dysphagia alone, a clinical goal of palliative chemotherapy, may provide a false estimate of the potential antitumor efficacy of chemotherapy as it may occur with even minimal antitumor response seen on barium esophagram. However, reliable assessment of response in the primary lesion has been reported in a series of patients in which the radiographic response of the primary tumor to therapy was correlated with response determined endoscopically or pathologically confirmed at surgery.[14,15] Use of the recently available technique of endoscopic ultrasonography may provide greater ability to evaluate local regional disease in the esophagus, particularly the degree of local tumor extension by T stage and detection of regional lymph node involvement.[16,17] Evaluation by endoscopic ultrasound is increasingly being used in clinical trials for staging and response evaluation.

Single-agent chemotherapy trials

The results of reported clinical trials for single chemotherapeutic agents in esophageal carcinoma are summarized in Table 1. Seventeen single agents have undergone systematic evaluation in phase I–II clinical trials. As can be seen from Table 1, modest antitumor activity for a broad range of chemotherapy drugs is seen in esophageal carcinoma, appearing fairly consistent when comparing single agents. Early studies evaluated patients with epidermoid carcinoma, but more recent studies have included patients with adenocarcinoma reflecting the increasing incidence of this disease. The rationale for treating both epidermoid and adenocarcinoma on the same clinical protocols is the similar natural history of the diseases, characterized by early widespread systemic disease dissemination. A precedent exists in clinical trials with non-small cell lung cancer.[18] Although both esophageal epidermoid and adenocarcinoma are frequently treated on the same chemotherapy protocols, response proportions for the two histologies are generally reported separately.

Early trials, such as the studies of bleomycin, were performed on a small number of patients often in the context of broad phase I–II trials in diverse solid tumors. Such trials also included patients with prior, often extensive, chemotherapy treatment. More recent trials, however, have been larger phase II trials and have generally limited new drug evaluation to patients without prior chemotherapy exposure. Recent studies have also employed a population size large enough to establish with some degree of statistical significance a major antitumor response.

Antibiotics

The antitumor antibiotics bleomycin, mitomycin C and doxorubicin have been studied in epidermoid carcinoma of the esophagus with response proportions ranging from 15 to 26% (pooled from multiple clinical trials). In two separate trials of doxorubicin, a difference in response proportion was noted (33 versus 5%). In the former study, reported by Kolaric *et al.*,[30] patients with locally advanced, inoperable disease were treated with doxorubicin at a dose of 40 mg/m^2 daily for two consecutive days, repeated every 3 weeks. Six of 18 patients treated had a major response (33%, 95% confidence intervals 11–55%), with the average duration of response 3.2 months. The latter trial treated patients with advanced metastatic disease with a lower dose of doxorubicin, 60 mg/m^2 given every 3 weeks; the trial, conducted by ECOG, was part of a randomized three-arm study in which patients received either doxorubicin, 5-fluorouracil (5-FU)

Table 1. Single-agent chemotherapy

	Cell type	*N*	*N* resp (%)	95% CI (%)	References
Antibiotics					
bleomycin	E	80	12 (15)	7–23	19–25
mitomycin	E	58	15 (26)	15–37	26–28
doxorubicin	E	38	7 (18)	5–31	29,30
idarubicin	A	16	1 (6)	0–18	31
amonafide	E	14	1 (7)	0–20	32
Antimetabolites					
5-FU	E	26	4 (15)	1–29	29
5-FU	A + E	13	11 (85)	60–100	33
methotrexate	E	65	23 (35)	24–47	29,34
DCM	E	22	0	<15	35
trimetrexate	E	20	2 (10)	1–19	36
aminothidiazole	E	23	0	<15	37
Plant alkaloids					
vindesine	E	86	19 (22)	14–32	38–41
etoposide	E + A	27	0	<15	42,43
	E	26	5 (19)	4–34	44
Heavy Metals					
cisplatin	E	152	42 (27.6)	20–35	45–48
	A	12	1 (8)	0–26	49
carboplatin	E	59	3 (5)	0–11	50–52
	A	11	1 (9)	0–26	53
Alkylating Agents					
ifosphamide	E	22	2 (8)	1–23	54
Other Drugs					
CCNU	E	19	3 (16)	0–32	55
MGBG	E	45	9 (20)	8–31	56,57

N = number patients, *N* resp = number of responding patients, CI = confidence interval, E = epidermoid, A = adenocarcinoma, DCM = dichloromethotrexate, CCNU = lomustine, MGBG = mitoguazone.

or methotrexate, with non-responders crossing over to the other treatment arms.[29] None of 16 previously untreated patients responded to doxorubicin and one of four previously treated crossover patients responded (5%, 95% confidence intervals 0–15%). Although the difference in response proportions in the two trials may be attributable to patient selection (local regional versus metastatic disease) or dosage of doxorubicin delivered, the difference may not be statistically significant as the 95% confidence limits of the two response proportions overlap.

Trials of antitumor antibiotics are ongoing. The anthracycline idarubicin was studied in metastatic esophageal adenocarcinoma and showed minimal antitumor activity (6%).[31] Amonafide, an isoquinolinedione which acts as an intercalating agent, showed marginal antitumor activity (7%) in metastatic epidermoid carcinoma with severe myelosuppressive toxicity.[32]

Antimetabolites

Antimetabolites, given as single agents, have modest antitumor activity (10–35%). 5-FU as a single agent was studied in two phase II trials, with widely disparate response proportions observed. In the first trial, the 5-FU arm of the three-arm ECOG trial discussed above, patients with metastatic disease were treated by bolus 5-FU given at a dose of 500 mg/m^2 daily for five consecutive days, repeated every 5 weeks.[29] Four of 26 previously untreated patients had a major response (15%), lasting 5–26 weeks. A higher response proportion was observed in the trial reported by Lokich *et al.*, using a continuous intravenous infusion of 5-FU for 6 weeks at a dose of 300 mg/m^2/day.[33] The patients in this study had local regional disease only and were treated prior to definitive radiation therapy. Nine partial responses among 11 treated patients with epidermoid carcinoma and two

complete responses in patients with adenocarcinoma were observed (overall response 11 of 13, 85%). The reason for the striking difference in response proportions seen in the two trials is unclear, although the higher response proportion was seen in patients with local regional disease without distant metastases, receiving a continuous infusion rather than bolus dosing of 5-FU. The influence of dose and schedule of 5-FU on antitumor response in gastrointestinal malignancies is still under study and remains controversial.[57]

Methotrexate has been studied in two separate trials. In the ECOG trial in patients with advanced, metastatic disease, methotrexate was given at a dose of 40 mg/m^2/week.[29] Three major responses were seen in 26 previously untreated patients (12%). The response durations were brief, ranging from 8 to 15 weeks. Advani *et al.*, employing a higher dose of methotrexate, treated patients with locally advanced, unresectable disease with a dose of 200 mg/m^2 given on days 1 and 10.[34] Twenty of 41 evaluable patients showed major response (48%). Duration of the responses could not be determined as the patients went on to receive either local radiation therapy or surgery. The differences in response in the two trials again may be a reflection of patient selection and dose of drug administered. Interest in methotrexate and methotrexate analogues in the treatment of esophageal carcinoma continues, with two recent trials of methotrexate analogues reported in advanced metastatic disease. A phase II trial of dichloromethotrexate in epidermoid carcinoma showed inactivity for the drug with none of 22 patients responding.[35] Trimetrexate showed marginal activity with only two of 20 evaluable patients with epidermoid carcinoma responding (10%); toxicity was prohibitive with half of the patients treated experiencing severe myelosuppression.[36]

Novel antimetabolites continue to enter phase II trial evaluation. Aminothiadiazole, an inhibitor of the enzyme inosine monophosphate dehydrogenase which results in inhibition of *de novo* purine synthesis, was studied in 23 patients with advanced epidermoid carcinoma.[37] No antitumor responses were observed.

Plant alkaloids

Consistent antitumor responses have been observed with the vinca alkaloid vindesine. Response proportions of 20–25% have been reported by Bezwoda and Derman[39] and Kelsen *et al.*[38] in epidermoid carcinoma, and smaller trials have also reported antitumor activity.[40,41] The epidophyllotoxin etoposide (VP-16) has been studied in adenocarcinoma and epidermoid carcinoma. Kelsen *et al.* reported no activity in seven patients with adenocarcinoma and no major responses in 20 patients with epidermoid carcinoma when treated at a dose of 100–120 mg/m^2/day for 3 days given every 3 weeks, although the majority of the patients on these studies had received prior chemotherapy.[42,43] In a more recent study in previously untreated patients with epidermoid carcinoma, Harstrick *et al.* observed five partial responses in 26 patients (19%) treated with a higher dose of etoposide, 200 mg/m^2/day for 3 days every 3 weeks.[44] The median duration of response was 5 months and toxicity was limited to neutropenia.

The new antimicrotubule agent taxol, a drug with significant activity in breast and ovarian cancer, is currently under investigation in epidermoid and adenocarcinoma of the esophagus. Because head and neck and esophageal cancer respond to a similar spectrum of antitumor agents, a preliminary report of a phase II trial of taxol in epidermoid carcinoma of the head and neck indicating significant antitumor activity has raised particular interest in taxol.[58]

Surprisingly, neither vinblastine nor vincristine, commonly used vinca alkaloids, have had therapeutic trials as single agents in patients with epidermoid or adenocarcinoma of the esophagus.

Heavy metals

Fairly large phase II trials with cisplatin have indicated a response proportion of 15–20% in metastatic epidermoid carcinoma,[45–46] although one smaller trial had lesser activity.[47] Overall a major response proportion of 27.6% has been observed in 152 patients with local regional and metastatic epidermoid carcinoma treated with single agent cisplatin. A small number of patients with adenocarcinoma of the esophagus was treated in a broad phase II trial of cisplatin in upper gastrointestinal tract reported by Ajani *et al.*[49] Of 12 patients treated with 100 mg/m^2 given every 3–4 weeks, only one partial response (8%) was observed.

The cisplatin analogue carboplatin has generated interest in solid tumor clinical trials because of relative ease of administration and minimal neurologic or renal toxicity in comparison with cisplatin. Activity for carboplatin in esophageal

carcinoma, however, has been disappointing. Three phase II trials of carboplatin have shown inactivity for the drug in epidermoid carcinoma (0–9%).[50–52] A trial in adenocarcinoma also revealed limited antitumor activity, with one major response observed in 11 patients treated (9%).[53]

Summary

Other single agents have undergone phase II evaluation, including ifosphamide, lomustine and mitoguazone, with minimal to moderate antitumor activity (Table 1). In summary, the modest antitumor activity of single agents and the short duration of response underscore the importance of studying new antitumor agents. The variability in response proportions seen in different studies may be a function of the patient population studied (local regional versus metastatic disease), drug dose and schedule selected, and the degree of prior chemotherapy treatment of patients on study.

Combination chemotherapy

Early trials

With modest activity demonstrated for several single chemotherapy agents, multidrug programs have also been studied. In earlier trials, patients with both local regional and metastatic disease were treated on the same protocols, with patients with local regional disease usually going on to receive either surgery or radiation therapy. Virtually all studies share cisplatin as a common agent. Early trials combined bleomycin with cisplatin and other agents. Coonley *et al.* reported activity of bleomycin and cisplatin in 61 patients with epidermoid carcinoma, with a major response proportion of 15%;[60] comparable response proportions were seen in preoperative patients with local regional disease (given only one cycle of preoperative chemotherapy) and patients with advanced or metastatic disease. Duration of response ranged from 5 to 9.5 months. Three other smaller trials showed similar antitumor activity for the combination of bleomycin and cisplatin.[61–63] Overall a response proportion of 25.5% has been observed. Bleomycin in combination with doxorubicin had comparably modest antitumor activity.[64]

Cisplatin in combination with vindesine and bleomycin has been studied in three phase II trials and two phase III trials. In the largest phase II trial reported by Kelsen *et al.*[65] major responses were seen in 28 of 44 patients with local regional disease (63%) after one to two cycles of preoperative therapy, and eight of 24 patients (33%) with advanced or metastatic disease. Schlag *et al.* reported partial responses in 19 of 42 patients with local regional disease treated preoperatively (45%), with two complete pathologic responses (5%).[66] Dinwoodie *et al.* reported major responses in seven of 27 patients (29%) with advanced or metastatic disease.[67] In the phase III trial of Roth *et al.*[68] patients were randomized to surgery alone or to preoperative chemotherapy with cisplatin, vindesine and bleomycin: eight of 17 patients (47%) with local regional disease receiving preoperative chemotherapy had a major response, with one patient achieving a pathologic complete response (6%). Kelsen *et al.*[69] randomized patients to preoperative radiation therapy or chemotherapy: 21 of 38 patients receiving chemotherapy had a major response (55%) and three patients achieved a pathologic complete response (8%). Of a total of 192 patients treated with cisplatin, vindesine and bleomycin, 91 responded (47%), with consistently different response proportions seen between patients with local regional disease (54%) and metastatic disease (29%).

Cisplatin in combination with mitoguazone and vindesine or vinblastine was studied in three separate phase II trials, with one trial treating both adenocarcinoma and epidermoid carcinoma.[70–72] Overall 15 of 30 patients with local regional epidermoid cancer had a major response (50%) with two pathologic complete responses (7%) and 14 of 60 patients with advanced or metastatic disease had a major response (23%). A lower response proportion was seen in the small number of patients with local regional adenocarcinoma reported by Forastiere *et al.*, with five of 16 patients (31%) having a major response.[72] Duration of responses in metastatic disease was brief, lasting a median of 3–4 months. Other cisplatin-based combinations have been reported, including combinations with methotrexate and other agents, with response proportions of 20–76% in patients with metastatic and local regional disease (see Table 2).

Cisplatin and 5-FU

The combination of cisplatin and 5-FU given by continuous infusion for 4–5 days has been studied extensively, based primarily on activity of this regimen in epidermoid carcinoma of the head and

Table 2. Combination chemotherapy

Drug	Cell type	*N*	*N* resp (%)	95% CI (%)	Extent	References
DDP–Bleo	E	110	28 (25.5)	14–37	LM	60–63
Bleo–Dox	E	16	3 (19)	1–37	LM	64
DDP–VDS–Bleo	E	191	91 (47)	40–54	LM	65–69
DDP–VDS/VLB–MGBG	E	90	29 (32)	24–40	LM	70–72
	A	16	5 (31)	8–54	L	72
DDP–MTX	E	43	32 (74)	61–87	L	34
DDP–MTX–Bleo	E	41	13 (32)	18–46	LM	73,74
DDP–MTX–VCR	E	28	17 (61)	43–79	L	75
DDP–MTX–Pep	E	16	9 (56)	22–70	L	76
DDP–MTX–Bleo–MGBG	E	14	9 (64)	39–89	LM	77
DDP–Bleo–VCR–5-FU	E	10	6 (60)	30–90	L	78
DDP–Bleo–VP16	E	16	5 (31)	8–54	LM	79
DDP–VP16	E	15	3 (20)	0–40	L	80
DDP–CTX–VDS	E	23	8 (35)	16–54	L	81
DDP–CTX–VDS–CCNU	E	28	6 (21)	6–35	LM	81
DDP versus	E	89	NS (11)	—	LM	82
DDP–5-FU			NS (36)			
DDP–5-FU	E	238	116 (48.7)	43–55	LM	83–89
DDP–Dox–5-FU	E	21	7 (33)	13–53	LM	90
DDP–Dox–5-FU–VP16	E	24	17 (71)	53–89	L	91
DDP–5-FU–VP16	E	20	13 (65)	47–83	LM	92
DDP–5-FU–Bleo	E	43	23 (53)	38–68	LM	93
5-FU–LV	E	35	6 (17)	5–29	LM	94
DDP–5-FU–LV	E	56	27 (48.2)	37–59	LM	95–97
DDP–5-FU–LV–VP16	E	38	22 (58)	42–73	LM	98
5-FU–IFN-α	A + E	37	10 (27)	13–41	LM	99
5-FU–IFN-α–DDP	A + E	15	8 (53)	28–78	LM	100
CBDCA–VLB	E	16	0		LM	101
CBDCA–DDP–5-FU	A + E	14	10 (71)	47–95	LM	102

N = number patients, *N* resp = number of responding patients, CI = confidence interval, DDP = cisplatin, Bleo = bleomycin, E = epidermoid, A = adenocarcinoma, Dox = doxorubicin, VDS = vindesine, VLB = vinblastine, MGBG = mitoguazone, MTX = methotrexate, VCR = vincristine, Pep = peplomycin, CBDCA = carboplatin, CTX = cyclophosphamide, CCNU = lomustine, LV = leucovorin.

neck, and with interest waning in the use of bleomycin containing-regimens because of pulmonary toxicity observed in surgical and radiation therapy protocols. Toxicity observed for the combination of cisplatin and 5-FU, mainly mucositis and myelosuppression, has been substantial but tolerable. Kies *et al.* reported the first use of 5-FU and cisplatin in local regional epidermoid carcinoma of the esophagus, with 11 major responses observed in 26 patients treated with three cycles preoperatively (42%).[83–84] The duration of response was indeterminate because most of the patients underwent resection or went on to receive radiotherapy. Subsequent reports have noted similar response proportions in patients treated predominantly with local regional disease.[85–89] Of a total of 238 patients treated with epidermoid carcinoma, 116 (48.7%) achieved a major response. Of 201 patients with local regional disease, 103 responded (51.2%) and occasional pathologic complete responses were observed in patients treated preoperatively (14 patients, 7.0%). In the recently reported series by Vignoud *et al.*,[87] 48 patients with local regional disease were treated with a more dose intensive schedule of infusional 5-FU given at a dose of 1 g/m^2/day for 4 days and cisplatin at a dose of 100 mg/m^2 on day 1, recycled every 14 days for 3 cycles preoperatively. Thirty-two major responses were seen (66%) including five pathologic complete responses (10%). The addition of doxorubicin[90] or doxorubicin and VP-16[91] to 5-FU and cisplatin has also been reported in small series of patients, with the 95% confidence limits of the response proportions comparable with 5-FU and cisplatin alone.

Despite the increasingly common use in the community of the combination of 5-FU and cisplatin for the treatment of esophageal carcinoma, only one trial has directly addressed the issue of comparative efficacy of single agent cisplatin versus

the combination of 5-FU and cisplatin, published only in abstract form.[82] Of 89 patients with unresectable or metastatic epidermoid carcinoma randomly assigned to receive cisplatin alone or the combination of cisplatin and 5-FU, a greater major response proportion was observed for the combination (36 versus 11%), but this did not result in any significant difference in survival.

5-FU and biodmodulation

Because of the use of 5-FU and cisplatin in the treatment of esophageal carcinoma, there has been extensive interest in the use of other agents to biomodulate the antitumor activity of 5-FU. Leucovorin, which enhances the cytotoxic activity of 5-FU by potentiating inhibition of the enzyme thymidylate synthetase, enhances the clinical antitumor response in patients with colorectal carcinoma.[103] Leucovorin as a potential biomodulator of 5-FU antitumor activity in esophageal epidermoid carcinoma was recently studied by Alberts *et el.*,[94] using the Mayo Clinic regimen of bolus 5-FU given at a dose of 425 mg/m^2/day for 5 days with low dose leucoverin given at a dose of 20 mg/m^2/day for 5 days. Of 35 patients with metastatic or locally advanced epidermoid carcinoma, six achieved a major response (17%) with a median duration of response of 32 weeks. No improvement was seen in antitumor response over the reported experience with single agent 5-FU. Cisplatin in combination with infusional 5-FU and leucovorin was studied in 56 patients with locally advanced or metastatic epidermoid carcinoma[95–97] and 27 patients experienced a major response (48.2%), no different from the results achieved without leucovorin (48.7%). The addition of etoposide to the three-drug regimen also did not appear to improve antitumor response,[98] although etoposide is active as a single agent in previously untreated patients with epidermoid carcinoma (Table 1).

Interferon (IFN)-α2a (IFN-α) as a potential biomodulator of 5-FU has been the study of two recently published phase II trials, based on the prior report of activity of the combination of 5-FU and IFN-α in colorectal carcinoma.[103] Biomodulation of 5-FU by IFN-α in laboratory studies occurs by inhibition of thymidylate synthetase expression[104] and in patients the pharmacokinetics of FU may be altered by the coadministration of IFN-α.[105] In patients with metastatic or unresectable disease, Kelsen *et al.* studied 5-FU given by continuous infusion for 5 days at a dose of 750 mg/m^2/day, followed by weekly outpatient bolus 5-FU at the same dose, given together with IFN-α at a dose of 9×10^6 units by subcutaneous injection three times per week.[99] Complete and partial responses were seen in 10 of 37 patients (27%) with adenocarcinoma and epidermoid carcinoma, with a median response duration of 6.4 months. The 95% confidence limits of the response proportion seen in this study overlapped the response seen for cisplatin-containing regimens. Kelsen *et al.* subsequently studied the combination of cisplatin, 5-FU and IFN-α in patients with metastatic or unresectable disease,[100] and a preliminary report of this study has shown activity in 53% of patients, suggesting significant activity for this regimen in advanced or metastatic disease.

Summary

In summary, cisplatin-based combination chemotherapy has yielded modest antitumor activity in metastatic epidermoid carcinoma of the esophagus in the range of 25–35%. Response proportions in local regional disease are consistently higher (45–75%). Although the number of studies in adenocarcinoma of the esophagus is limited, activity is also seen for cisplatin-based chemotherapy. With the exception of one study comparing 5-FU alone with the combination of 5-FU and cisplatin, there are no random assignment trials comparing one combination chemotherapy regimen with another, or comparing regimens with or without cisplatin. Leucovorin does not appear to increase antitumor activity of 5-FU-containing regimens and the study of IFN-α in combination chemotherapy continues. Toxicity of these regimens is moderately severe and manageable, with mucositis and myelosuppression predominating. Response durations, evaluable only in patients who do not go on to surgery or radiation therapy, are generally brief, and outside of palliation of disease a major impact of chemotherapy alone on survival is unclear.

Neoadjuvant chemotherapy and radiotherapy

Clinical trials of systemic chemotherapy given preoperatively in esophagus cancer, also termed neoadjuvant or primary chemotherapy, have been

undertaken largely because of the disappointing results achieved with conventional surgery or radiation therapy alone. Such combined modality trials employing chemotherapy have taken one of three different approaches: (i) chemotherapy followed by a planned surgical procedure, (ii) chemotherapy given concurrently with radiation therapy, followed by surgery, and (iii) chemotherapy and radiation therapy without subsequent surgical intervention. The rationale, both preclinical and clinical, for neoadjuvant chemotherapy has been reviewed.[106] For esophageal cancer patients, the approach of preoperative chemotherapy offers several potential clinical benefits including enhancing resectability by downstaging the primary tumor, and assessing directly the antitumor efficacy of chemotherapy and thus making the endpoint of adjuvant therapy more precise. Giving chemotherapy early on in the course of the disease also has the advantage of treating micrometastatic disease when chemotherapy is likely to have its greatest impact, given the limited effectiveness of systemic therapy to treat clinically apparent metastatic disease. A disadvantage of preoperative chemotherapy is the delay in achieving local control of disease. The rationale for concomitant chemotherapy and radiation therapy has also been reviewed.[107] Concurrent chemoradiotherapy potentially allows the achievement of enhanced local control as well as treating systemic micrometastases.

Chemotherapy followed by surgery

The objective antitumor response seen in patients with local regional esophageal carcinoma treated with combination chemotherapy preoperatively was discussed above. The use of preoperative chemotherapy in esophageal cancer has been reviewed in detail by Kelsen.[108] To date, at least 16 trials involving more than 600 patients have been reported. These studies have been primarily single-arm phase II trials in selected patients. Operative mortality after preoperative chemotherapy has been comparable with surgical series alone (0–15%). Operability after chemotherapy has ranged from 54 to 100% and resectability of operated patients has ranged from 60 to 95%, indicating that the administration of preoperative chemotherapy is safe and without a demonstrable adverse effect on surgical outcome. However, the overall survival of patients treated with preoperative chemotherapy has been disappointing, with a median survival ranging from 10 to 16 months in larger series. The longest follow has been reported by Kelsen *et al.*[109] in a series of 34 patients with epidermoid carcinoma, treated with one or two cycles of preoperative cisplatin, vindesine and bleomycin. After a minimum follow up of 6 years (median 7 years), 17.5% of patients were alive and free of disease, and there were no recurrences after 3.5 years. In several trials, a trend toward improved median survival has been observed in patients manifesting a major objective response to chemotherapy, but whether response to therapy is independent of other favorable prognostic factors is unclear. The duration of chemotherapy delivered in trials has undergone evolution: while earlier trials administered only one or two cycles of chemotherapy preoperatively without subsequent postoperative therapy, more recent trials have given up to three or more cycles of preoperative therapy and two to three cycles of postoperative chemotherapy. The treatment outcome in earlier and more recent trials may therefore not be directly comparable, particularly with regard to the impact of additional cycles of systemic therapy on the systemic recurrence of disease.

Ongoing random assignment trials with a surgery-only control arm will more clearly establish the role of preoperative chemotherapy in the treatment of local regional esophageal carcinoma. Two phase III trials employing a surgery-alone arm versus preoperative chemotherapy have been published. Roth *et al.* randomly assigned 39 patients to surgery alone or two preoperative cycles of vindesine, cisplatin and bleomycin followed postoperatively by maintenance chemotherapy.[68] Although operative morbidity and median survival (9 months) were not different in the surgery-alone versus chemotherapy arm, the median survival was longer in patients treated with chemotherapy who manifested an objective antitumor response. A larger recently published random assignment trial with a surgery-alone treatment arm by Nygaard *et al.*[110] studied preoperative cisplatin and bleomycin, a regimen with one of the lowest reported antitumor responses of the cisplatin-based chemotherapy combinations used in prior phase II trials (Table 2). Two additional treatment arms employed preoperative radiotherapy, either given alone or concurrently with chemotherapy with cisplatin and bleomycin. Operability, resectability and operative mortality were comparable in all treatment arms. A benefit in median survival was observed in the patients receiving radiotherapy with or without

chemotherapy, but no survival benefit was seen in the patients receiving preoperative chemotherapy. The use of a probably suboptimal chemotherapy regimen in this study may have diminished the effect of chemotherapy. However, a recently reported study using single agent cisplatin reported significant preoperative antitumor activity (55%) in the absence of a combination with other drugs.[48] A conclusive evaluation of preoperative chemotherapy using the best currently available combination chemotherapy regimen awaits the completion of ongoing random assignment clinical trials. An intergroup trial sponsored by the RTOG is ongoing, in which patients are randomly assigned to surgery alone or two three preoperative cycles of 5-FU and cisplatin followed by surgery followed by two postoperative cycles of 5-FU and cisplatin. Currently the use of preoperative chemotherapy in esophageal carcinoma remains investigational.

Chemoradiotherapy with or without surgery

The intensification of radiotherapy with concurrent chemotherapy used as a radiation sensitizer, either in the preoperative setting or as definitive local therapy, has been the subject of many single-arm phase II studies. More than 20 trials studying over 450 patients have been reported. The chemotherapy in most series has combined cisplatin or mitomycin C with 5-FU given by continuous infusion. Although survival has been then primary endpoint of the majority of these trials, major antitumor responses have been reported in 40–75% of patients, with up to 25% pathologic complete responses seen at esophagectomy. Median survival in these series has been disappointing, ranging from 11 to 22 months. The contribution of esophagectomy in these trials is unclear, particularly in light of the report by Leichman *et al.*[111] In long-term follow up of a series of patients with a pathologic complete response to chemoradiation therapy, determined at esophagectomy, all eventually died of metastatic disease without evidence of local failure. This observation raised the issue of use of chemoradiation without subsequent esophagectomy. A non-surgical, random assignment trial in local regional esophageal carcinoma comparing radiation therapy alone with radiation given with concurrent 5-FU and cisplatin was recently published by Herskovic *et al.*[113] With a median follow up of 18 months, a highly significant survival benefit at 1 and 2 years was demonstrated for chemoradiation versus radiation therapy alone. A recent update of the results of this trial continues to demonstrate a significant survival benefit for chemoradiation therapy versus radiation therapy alone: 33% of patients treated with chemoradiation were alive compared to only 5% of patients treated with radiation therapy alone, with a median follow up of greater than 36 months.[112] A random assignment trial comparing preoperative chemoradiation therapy with surgery alone is ongoing at the University of Michigan at Ann Arbor.

Future directions

The search for effective antitumor agents in the treatment of esophageal cancer continues, given the modest activity of currently available agents and brief duration of antitumor responses observed. Future strategies in the treatment of esophageal carcinoma will undoubtedly be based upon advances in the understanding of the biochemistry and molecular biology of the disease. Ongoing studies indicate a potential role for oncogenes and tumor suppressor genes in the mechanism of tumorigenesis, and indicate that these factors may be important biologic prognostic factors predicting eventual clinical outcome. Laboratory studies have revealed evidence of enhanced expression and amplification of the epidermal growth factor (EGF) receptor gene[114,115] and amplification of the c-*myc* oncogene[115] in esophageal epidermoid carcinoma. Immunohistochemical studies of EGF and EGF receptor (EGFR) protein expression in resected esophageal epidermoid cancers, have shown that increased degrees of expression of EGF or EGFR protein correlate with a worse outcome with poorer survival.[116] The tumor suppressor gene *p53* has been studied in esophageal carcinoma with demonstration of *p53* mutations in epidermoid and adenocarcinoma and in the premalignant lesion of Barret's epithelium.[117,118] Loss of heterozygosity of the retinoblastoma tumor suppressor gene locus in human epidermoid and adenocarcinoma of the esophagus has also been demonstrated.[119] The *int-2* oncogene, the fibroblast growth factor-related proto-oncogene, has been shown to be co-amplified with the locus *hst-1*, with the co-amplification correlating with poorer survival and a higher incidence of eventual systemic metastasis in patients resected for cure.[120] The ultimate goal in studying potential biochemical perturbation of normal growth factor receptor and growth signal transduction pathways is the identification of novel targets

for chemotherapeutic agents of the future. Overcoming tumor cell drug resistance to conventional chemotherapeutic agents is also the study of ongoing laboratory and clinical trials. A recent report evaluating mechanisms of potential chemotherapeutic drug resistance of esophageal epidermoid carcinoma cell lines *in vitro* indicated that the multidrug resistance phenotype, mediated by the drug efflux pump P-glycoprotein, may mediate drug resistance and may be overcome by pharmacologic intervention.[121] Overcoming drug resistance by exploring known biochemical mechanisms of antineoplastic drug resistance, such as the multidrug resistance phenotype, is the subject of an increasing number of clinical trials in solid tumors.

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