Review

Palliative Chemotherapy for Recurrent and Metastatic Esophageal Cancer

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Abstract. *More than two-thirds of patients diagnosed with esophageal cancer will have unresectable disease. The objective of this article is to review the clinical trials utilizing cytotoxic chemotherapy in patients with recurrent and metastatic esophageal cancer. A computerized (MEDLINE) search was performed to identify papers published on this topic between 1966 and 2007. A total of 96 trials were subsequently identified. Two randomized trials compared palliative chemotherapy with best supportive care in 180 patients with advanced esophageal cancer. Effectiveness and side-effects were evaluated in 49 phase II studies and 3 randomized phase III trials. Combination chemotherapy as compared to monochemotherapy is associated with significantly higher response rates but nevertheless results in similar survival. CF (cisplatin and 5-fluorouracil) currently represents one of the most effective regimens for advanced esophageal cancer, while among the newer combinations, irinotecan or taxane-based regimens have also given promising results. Prognosis for the majority of patients, however, remains poor as increases in survival were moderate at best.*

Esophageal cancer is the seventh leading cause of death in the Western world. More than two-thirds of patients will have unresectable disease at the time of diagnosis (1). Even patients with resectable disease have a high rate of both local and distant recurrence and the expected median survival is only 24 months, with a 5-year survival rate lower than 30% (2). Whereas squamous cell esophageal carcinoma is still the most common histology, the incidence of adenocarcinoma is continuously increasing.

Palliative treatment is the only option for patients with advanced esophageal cancer with the goal of controlling cancer-related symptoms and prolonging survival without compromising the patient's quality of life. This can be achieved with chemotherapy, radiation therapy, surgery or best supportive care. A variety of single agents and combination regimens have been evaluated in patients with advanced carcinoma of the esophagus since the early 1970s.

The objective of this article is to briefly review the clinical trials available in the current literature which utilized cytotoxic chemotherapy in patients with advanced, *i.e.* locally inoperable or metastatic esophageal cancer.

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Methods

Using a computerized (MEDLINE) and manual search, we identified a total of 96 reports of palliative chemotherapy performed in patients with recurrent or metastatic esophageal cancer. Only papers with an English abstract were included and no effort was made to search for unpublished trials, thus a slight degree of publication bias cannot be excluded. Chemotherapy was defined as use of a cytotoxic drug or drug combination, distinct from immunotherapy and radiotherapy. Combinations of chemotherapy with radiotherapy were not included. Tumor responses were analyzed as reported by the authors, but only patients achieving at least a partial remission (PR) qualified as responders.

Single Agent Chemotherapy

Chemotherapy as a single modality has largely been used for palliation of patients with advanced esophageal cancer. The majority of these trials enrolled patients with squamous cell carcinomas, but due to the rising incidence of adenocarcinoma more recent trials have also included patients with this type of histology.

Several reviews outline the results of single-agent studies; these are summarized in Table I. The cumulative response rate for any one drug is low, of the order of 15% to 35%, and there is no indication of survival benefit (3-32).

Table I. *Selected monochemotherapy in advanced esophageal cancer.*

Agent	Histology	No. of patients	Response rate	Reference
BLM	SCC + AC	5	20%	(7)
BLM	SCC + AC	20	20%	(8)
BLM	SCC + AC	4	0	(9)
BLM	SCC	3	33%	(10)
BLM	SCC	14	0	(11)
BLM	SCC	29	14%	(12)
BLM	SCC + AC	15	27%	(13)
MMC	SCC	24	42%	(16)
MMC	SCC	7	14%	(17)
MTX	SCC	26	12%	(15)
MTX	SCC	41	49%	(19)
5-FU	SCC	26	15%	(15)
5-FU	SCC + AC	13	85%	(14)
VDS	SCC	52	27%	(27)
VDS	SCC	34	22%	(25)
ADM	SCC + AC	13	38%	(18)
ADM	SCC	20	5%	(15)
VINO	SCC	152	28%	(21, 22, 100)
VINO	SCC	30	20%	(31)
CDDP	SCC + AC	17	6%	(20)
CDDP	SCC	24	25%	(16)
CDDP	SCC	35	26%	(22)
CDDP	SCC	15	73%	(24)
CDDP	AC	12	1%	(37)
CBP	SCC + AC	30	7%	(36)
CBP	SCC	11	14%	(39)
CBP	SCC	18	0	(40)
VP-16	SCC	20	0	(47)
DOCE	SCC + AC	52	20%	(45)
PAC	AC	32	34%	(3)
	SCC	18	28%	
DOCE	AC	8	20%	(43)
VINO	SCC	17	25%	(101)

AC: adenocarcinoma; ADM: adriamycin/doxorubicin; BLM: bleomycin; CAPE: capecitabine; CBP: carboplatin; CDDP: cisplatin; CPT-11: irinotecan; DOCE: docetaxel; EPI: epirubicin; 5-FU: 5-fluorouracil; GEM: gemcitabine; IFN: alpha 2a-interferon; LV: leucovorin; MGBG: methylglyoxal-bis-guanylhydrazone; MMC: mitomycin-C; MTX: methotrexate; PAC: paclitaxel; RA: retinoic acid; RALT: raltitrexed; SCC: squamous cell carcinoma; VBL: vinblastine; VDS: vindesine; VINO: vinorelbine; VP-16: etoposide.

Bleomycin, 5-fluorouracil (5-FU), mitomycin, and cisplatin are the four agents used most often because of their activity as single agents or in combination, and their additive or synergistic effects with radiation.

Bleomycin

Bleomycin was tested in 80 patients using doses of 15 to 30 mg/m^2 twice weekly or 10 to 20 mg/m^2 daily (7, 9-13, 33). The cumulative response rate was 15% in patients with squamous cell carcinoma. A randomized trial comparing chemotherapy with bleomycin and best supportive care did not demonstrate a survival advantage (34). Because of the potential for pulmonary toxicity, bleomycin is no longer included in combination regimens, having been replaced by 5-FU.

Platinum agents. There are several studies reported with cisplatin. Out of them, five used doses ranging from 50 to 120 mg/m^2 every 3 to 4 weeks. The cumulative response rate from these studies was 21% (20-22, 35, 36). Administration of the drug as a single bolus dose once every 3 weeks or in a divided dose over 5 days every 3 weeks appears equally efficacious. In one small trial with 51 patients, of whom 12 had metastatic esophageal adenocarcinoma, cisplatin produced a low response rate of 6% in previously treated patients (37). In contrast, another study with a more dose-intense schedule of cisplatin 120 mg/m^2 every two weeks (24) observed a 73% response rate in 15 patients before surgery. Although no complete responses were seen, these data support the observation that sensitivity to chemotherapy is greater in newly diagnosed patients. In one randomized phase II study, 92 patients with locally advanced or metastatic squamous cell carcinoma were randomized to receive either cisplatin with continuously infused fluorouracil every 3 weeks or cisplatin alone (38). Although the response rate for the combination was higher (35% *vs.* 19%), survival was similar for both groups (33 *vs.* 28 weeks). But, noteworthy, the study was not empowered to detect a meaningful difference in survival.

Several phase II trials that investigated the activity of carboplatin in squamous cell carcinoma and adenocarcinoma cases found only limited antitumor activity for both histological subtypes (36, 39-41). Therefore, carboplatin should not be substituted for cisplatin.

Taxanes. The taxane paclitaxel is the first entirely new compound to be adequately tested in both adenocarcinoma and squamous cell carcinoma of the esophagus. Paclitaxel promotes the stabilization of microtubules and is a cycle-specific agent affecting cells in the G(2)/M phase (42). Paclitaxel as monotherapy has been evaluated as first-line therapy using the maximum tolerable dose of 250 mg/m^2 administered by 24-hour infusion every 3 weeks (32). A 34% response rate was observed in 33 patients with adenocarcinoma and a 28% response rate in 18 patients with squamous cell carcinoma of the esophagus with an overall response rate of 32%. The dose-limiting toxicity is myelosuppression, primarily neutropenia.

There are no completed studies using either shorter or longer infusion schedules such as 1, 3, and 96 hours except one small phase II study in patients previously treated for metastatic disease, which failed to demonstrate activity. The data emerging from studies in other organ sites suggest that longer infusion schedules may be more efficacious.

When evaluated as part of an Eastern Cooperative Oncology Group trial, docetaxel produced a response rate of 17% in patients with previously untreated metastatic esophageal or gastric adenocarcinoma (43). In another Phase II trial of docetaxel, a response rate of 18% was seen in chemonaïve patients *versus* 0% in previously treated patients (44). In a study by Muro *et al.* the majority of patients had squamous cell carcinoma (45); 20% achieved a partial response, of whom more than half had had a prior platinum-based chemotherapy. In all trials it was evident that careful management of neutropenia is needed.

Alkaloids. The vinca alkaloid vindesine was studied in several phase II trials and demonstrated reproducible antitumor activity in cases of squamous cell carcinoma (25-27). Vindesine and mitoguazone (methyl-GAG, MGBG) were also used in combination regimens given preoperatively in the early 1980s but because of toxicity they are not recommended for use (28-30).

Vinorelbine has been studied for treatment of squamous cell carcinoma. It has less neurotoxicity compared with vincristine and vinblastine, but neutropenia is the dose-limiting side-effect. The EORTC reported a 20% response rate in 30 untreated patients with metastatic squamous cell cancer of the esophagus (31).

Topoisomerase inhibitor. Etoposide, an inhibitor of type II topoisomerase, demonstrated a response rate of 19% in one trial (46). In contrast, other studies showed response rates of less than 5% (47, 48). The type I topoisomerase inhibitor irinotecan has recently shown promising activity in a number of gastrointestinal malignancies, including gastric and esophageal cancer. In a pilot study, two out of nine mostly pretreated patients showed a partial response, of whom one had a adenocarcinoma and one a squamous cell carcinoma (49).

Antimetabolites. 5-FU was studied by Lokich using a protracted infusion schedule for 6 weeks in patients with newly diagnosed esophageal cancer (14). Assessment with endoscopy and barium esophagogram demonstrated a response in 85%. These results are in contrast with an ECOG trial in which a 15% response rate was observed in previously treated patients given intermittent bolus 5-FU (15). Similarly, methotrexate has a reported response rate of 12% in patients with recurrent squamous cell esophageal cancer and a 48% response rate in newly diagnosed patients (15). Other drugs that have been adequately tested in squamous cell cancer of the esophagus and have response rates of less than 5% are the methotrexate analogues dichloromethotrexate and trimetrexate, ifosfamide and gemcitabine (50-54).

Others. As single agents, the antitumor antibiotics mitomycin-C and doxorubicin demonstrated antitumor activity with response rates ranging from 14% to 38% in patients with squamous cell carcinoma (17, 18).

Combination Chemotherapy

Most of the drugs described above have also been studied in combination chemotherapy regimens. There are two randomized studies which compare combination chemotherapy with best supportive care (55, 56). In the study by Nicolaou *et al.* (56) were only 24 patients were included, so no meaningful conclusion can be drown. The study by Levard *et al.* (55) did not demonstrate a survival advantage. Nevertheless, several newer agents in combination with 5-FU or cisplatin show promising activity.

Combinations with platinum agents. Cisplatin-based combinations appear to be the best studied and demonstrate the most favorable response activity. The results of platinum-based combination chemotherapy regimens are detailed in Table II. Most series contain low numbers of patients and therefore the 95% confidence intervals are large. The duration of response is variable, but on average ranges from 3 to 6 months.

Kelsen and colleagues at Memorial Sloan-Kettering Cancer Center have the largest single institution experience testing combination chemotherapy (57, 58, 63-65). This group first evaluated cisplatin and infusional bleomycin in patients with squamous cell carcinoma observing a 17% response rate (57).

The most commonly used regimen is cisplatin 100 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2/d by continuous infusion. A 35% response rate was reported for patients with advanced squamous cell cancer of the esophagus (23). In a study by Hayashi *et al.* a dose of 20 mg/m^2 of cisplatin and 800 mg/m^2 of 5-FU was given by continuous infusion for 24 h on days 1-5 every 4 weeks (66). The overall response rate was 33.3% (12/36) with a median survival time of 201.5 days. Similar results were seen in a study by Caroli-Bosc *et al.* (67). Fifty-nine patients with measurable disease were treated with a weekly infusion of high dose 5-FU (2 or 2.6 g/m^2) plus leucovorin 500 mg/m^2 for 6 weeks and a bi-weekly dose of cisplatin (50 mg/m^2). The overall response rate was 33% and the median survival of 7.9 months. Somewhat higher response rates, in the 40% to 60% range, were reported from trials administering 2 to 3 cycles of cisplatin and 5-FU as neoadjuvant therapy. The difference may be related to better performance status, nutrition and smaller volume disease in operative candidates.

Attempts to substitute carboplatin for cisplatin have been unsuccessful. A phase II trial of carboplatin and vinblastine reported no responses in 16 patients, even though 11 with advanced, inoperable cancer were previously untreated and 15 patients had Karnofsky performance scores of 70% or

Table II. *Selected polychemotherapy in advanced esophageal cancer.*

Agent	Histology	No. of patients	Response rate	Reference
CDDP/BLM/MTX	SCC	9	44%	(61)
CDDP/5-FU/ADM	SCC	21	33%	(102)
CDDP/BLM	SCC	18	17%	(59)
CDDP/BLM/MTX	SCC	31	26%	(60)
CDDP/BLM/MTX/MGBG	SCC	9	55%	(103)
CDDP/VDS/BLM	SCC	24	33%	(58)
CDDP/VDS/BLM	SCC	27	29%	(59)
CDDP/VBL/ BLM	SCC + AC	51	29%	(58, 59)
CDDP/5-FU/Allopurinol	SCC	37	35%	(83)
CDDP/VDS/MGBG	SCC	20	40%	(58)
CDDP/VBL/MGBG	SCC	36	11%	(104)
CBP/VBL	SCC	16	0	(64)
CDDP/5-FU	SCC	35	34%	(105)
CDDP/MTX	SCC	42	76%	(19)
CDDP/5-FU/LV/VP-16	SCC + AC	38	45%	(106)
5-FU/IFN	SCC	31	26%	(84, 85)
	AC	24	29%	
CDDP/5-FU/IFN	SCC	11	73%	(65)
	AC	15	33%	
CDDP/VP-16	SCC + AC	92	48%	(107, 108)
CDDP/5-FU	SCC	44	35%	(23)
CDDP	SCC	44	19%	
VP-16/MMC	AC	15	13%	(109)
CDDP/ PAC	SCC	10	60%	(63)
	AC	27	37%	
CDDP/ PAC	SCC + AC	58	52%	(110)
5-FU/ADM/MTX	SCC + AC	88	21%	(73)
EPI/CDDPI5-FU	SCC + AC	90	45%	
CDDP/ PAC	SCC	20	40%	(111)
	AC	8	40%	
CDDP/5-FU/ PAC	SCC	30	50%	(81)
	AC	30	47%	
CDDP/5-FU	SCC + AC	72	30%-	(55)
Control	SCC + AC	84		
CBP/ PAC	SCC	9	44%	(112)
CDDP/5-FU	SCC	20	55%	(113)
CDDP/CPT-11	SCC	35	57%	(93)
	AC	20		
CDDP/5-FU/LV	SCC + AC	30	27%	(114)
CDDP/ PAC	SCC	64	52%	(115)
CDDP/PAC/VP-16	SCC	22	100%	(116)
	AC	22		
EPI/CDDP/RALT	SCC + AC	21	29%	(75)
CDDP/5-FU	SCC	42	33%	(66)
CDDP/5-FU	SCC	59	33%	(67)
CDDP/RA/IFN	SCC	38	21%	(90)
CDDP/VP-16/5-FU/LV	SCC	69	34%	(74)
5-FU	SCC + AC	127	16%	(91)
5-FU/MMC	SCC + AC	127	19%	
5-FU/IFN	SCC	33	61%	(89)
	AC	7	29%	
CDDP/VINO	SCC	24	34%	(68)
EPI/CDDP/5-FU	SCC + AC	290	42%	(72)
MMC/CDDP/5-FU	SCC + AC	290	44%	
DOCE/CPT-11	SCC + AC	10	30%	(94)
DOCE/CPT-11	SCC + AC	24	12.5%	(95)
CDDP/GEM	SCC + AC	64	40%	(70)
PAC/CBP	SCC	35	43%	(77)
CDDP/GEM	SCC + AC	36	41%	(69)
CDDP/CPT-11	SCC + AC	39	36%	(117)
GEM/5-FU/LV	SCC + AC	35	31%	(92)
DOCE/CAPE	SCC + AC	24	46%	(82)

AC: adenocarcinoma; ADM: adriamycin/doxorubicin; BLM: bleomycin; CAPE: capecitabine; CBP: carboplatin; CDDP: cisplatin; CPT-11: irinotecan; DOCE: docetaxel; EPI: epirubicin; 5-FU: 5-fluorouracil; GEM: gemcitabine; IFN: alpha 2a-interferon; LV: leucovorin; MGBG: methylglyoxal-bis-guanylhydrazone; MMC: mitomycin-C; MTX: methotrexate; PAC: paclitaxel; RA: retinoic acid; RALT: raltitrexed; SCC: squamous cell carcinoma; VBL: vinblastine; VDS: vindesine; VINO: vinorelbine; VP-16: etoposide.

better (64). The results of this trial and phase II single-agent carboplatin trials indicate that carboplatin and cisplatin do not have comparable activity in carcinoma of the esophagus (36, 39-41).

The evaluation of the combination of cisplatin with vinorelbine was made by Conroy *et al.* in seventy-one untreated patients (68). A partial response was seen in 33% of patients and the median survival was 6.8 months.

The combination of cisplatin with gemcitabine was studied by Kroep *et al.* (69). Cisplatin (50 mg/m^2, days 1 and 8) followed by gemcitabine (800 mg/m^2, days 2, 9 and 16), every 4 weeks was administered in thirty-six chemonaïve patients with advanced adenocarcinoma (n=24) or squamous cell carcinoma (n=12). As expected, myelosuppression was the main toxicity. A total of 41% of patients had a major objective response and the median survival was 9.8 months. The same combination (gemcitabine 1000 mg/m^2 on days 1, 8 and 15 and cisplatin 100 mg/m^2 on day 15, every four weeks) was evaluated by Urba *et al.* (70). Out of 64 eligible patients, 26% had had prior chemotherapy. Survival at 3 months was 81% and at 1 year 20%; median survival was 7.3 months.

Older trials testing cisplatin, bleomycin, vindesine and cisplatin, MGBG and vindesine yielded response rates of 31% and 40% (58, 62). Three-drug cisplatin-based regimens tested by other investigators confirmed the response rate of 30% to 40% in this population (59-61).

Another triple combination chemotherapy with methotrexate, cisplatin and 5-FU achieved a partial response of 28% with median survival of 5 months (71). One of the largest trials included 580 patients with oesophagogastric cancer, 188 patients with esophageal cancer and 125 with cancer of the oesophagogastric junction (72). They were randomized to receive either ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 both every 3 weeks

and 5-FU 200 mg/m^2/d as CI) or MCF (mitomycin 7 mg/m^2 every 6 weeks, cisplatin 60 mg/m^2 every 3 weeks and 5-FU 300 mg/m^2/d as CI). The overall response rate (42.4% with ECF *vs.* 44.1% with MCF) and median survival (9.4 vs 8.7 months) were comparable, but quality of life was superior with ECF at 3 and 6 months.

A survival advantage of the ECF regimen was seen in a study by Webb and colleagues (73). They conducted a prospective randomized trial comparing EFC with a regimen consisting of 5-fluorouracil, doxorubicin and methotrexate (FAMTX). Out of the 256 eligible patients, 51 had esophageal cancer, 60 cancer of the oesophagogastric junction and 145 gastric cancer. The ECF regimen resulted in a survival advantage, 8.9 *versus* 5.7 months, with tolerable toxicity and better quality of life compared with the FAMTX regimen.

A median survival of 9.5 months was seen in sixty-nine patients receiving a combination of cisplatin, etoposid and 5-FU combined with folinic acid (74) with an overall response rate of 34%.

Twenty-one patients with advanced esophageal adenocarcinoma received first-line chemotherapy with cisplatin, epirubicin and tomudex (ECT) (75). The overall response rate was 29%, 4 (19%) patients had stable disease. Median time to progression was 19 weeks and median overall survival 18 weeks. There were three toxic deaths: two due to sepsis complicating neutropenia and one due to cardiorespiratory failure following drug induced enteritis. Nine patients experienced grade 3 or 4 neutropenia, two patients experienced grade 3 or 4 nausea and vomiting, and one patient had grade 4 diarrhea. The toxicity suggests that further evaluation in a randomized comparison to ECF is not appropriate.

Oxaliplatin is a novel antineopolastic platinum analog which is less nephrotoxic, less neurotoxic and less emetic compared to cisplatin. One phase II study evaluated the combination of oxaliplatin and 5-FU/LV in 34 patients with metastatic cancer of the esophagus or gastric cardia (76). Of the assessable patients, 40% had an objective response. The regimen was, except for neutropenia and cumulative peripheral neutropenia, well-tolerated.

Combinations with taxanes. Because paclitaxel is one of the most active single agents in esophageal cancer combination regimens were evaluated in several trials. In a study by El-Rayes *et al.,* 33 patients were treated with a combination of paclitaxel and carboplatin (77). The objective response rate was 43%, with a median survival time of 9 months. The major grade 3-4 toxicity observed was neutropenia, occurring in 17 patients (52%).

Several studies evaluated the combination of paclitaxel with cisplatin. Thirty-seven patients with advanced or locoregional disease were treated with a combination of paclitaxel (200 mg/m^2 as 24-h infusion, day 1) and cisplatin 75 mg/m^2 (day 2) every 3 weeks in a study by Kelsen *et al.* (63). Major objective responses were seen in 49% with similar response rates for patients with metastatic and locoregional disease. Similar results were seen in a study by Ilson *et al.* (78) (RR 44%) and Polee *et al*. (79) (43%) with the same combination in advanced esophageal cancer as first-line combination chemotherapy. In a study by Cho *et al.* 28 patients out of 32 (88%) had already been treated previously before they received biweekly paclitaxel (90 mg/m^2) followed by cisplatin (50 mg/m^2) (80). The objective response rate was 41%, with a median overall survival of 7 months.

The triple combination of paclitaxel combined with cisplatin and 5-FU has been evaluated as first-line therapy in 61 patients with advanced carcinoma of the esophagus (81). Thirty patients had adenocarcinoma and 31 patients had squamous cell carcinoma. A 48% response rate was observed in 60 patients, but severe stomatitis and neutropenia occurred in most. Comparable responses were seen in patients with adenocarcinoma (46%) and those with squamous cell carcinoma (54%), but a significantly higher complete response rate was observed in patients with squamous carcinoma (20%) compared with those with adenocarcinoma (3%).

Another trial assessed the efficacy, safety and feasibility of capecitabine in combination with docetaxel in 24 patients with metastatic oesophageal cancer (82). Intent-to-treat efficacy analysis showed an overall response rate of 46% and the median survival was 15.8 months.

Combinations with 5-FU. Modulation of 5-FU with allopurinol, as evaluated by DeBesi and co-workers, increased toxicity without improving efficacy (83). In contrast, three trials using interferon-alpha2-a as a biomodulator of 5-FU suggest a possible benefit (65, 84, 85). Preclinical data indicate synergistic cytolytic activity when interferon is combined with 5-FU (86, 87). The exact mechanism is unclear but may result from interferon stimulation of thymidine phosphorylase, which increases the conversion of 5-FU to its active metabolite fluoro-deoxyuridylate. Kelsen and colleagues treated 37 patients (19 squamous cell carcinoma, 16 adenocarcinoma) with 9 million units of interferon-alpha2-a three times weekly and a 5-day continuous infusion of 5-FU 750 mg/m^2/d, followed by weekly bolus dosing (84). The overall response rate was 27%, 21% in squamous cell patients and 38% in adenocarcinoma patients, and the median duration of response was 6.4 months. Toxicity was primarily fatigue, which necessitated interferon dose reduction in nearly all patients. Wadler *et al.*, using the same regimen, observed a 25% response rate in a similar population (85). In both studies, durable responses (14 to 18 months) occurred in patients with bulky disease.

Building on this experience, Ilson *et al.* added interferon-alpha2-a to cisplatin and 5-FU (65). In 26 patients with metastatic or locally advance disease the response rate was 50%. The response proportion by histology was noteworthy: 8 of 11 patients (73%) with squamous cell carcinoma and 5/15 patients (33%) with adenocarcinoma. The same combination was evaluated by Wadler and colleagues (88). Out of 23 eligible patients, 15 (65%) had a major response with a median survival of 8.6 months. These results were confirmed in a study by Bazarbashi *et al.* who enrolled forty patients (33 had squamous carcinoma and 7 adenocarcinoma) (89). Five patients (13%) achieved a complete response and 17 (42%) achieved a partial response, yielding an overall response rate of 55%. Response rates for squamous and adeno histology were 61% and 29%, respectively. Median survival was 6.4 months.

A lower response rate was seen in thirty-eight patients with advanced squamous cell carcinoma who were enrolled in a phase II study to investigate an association of low-dose all-*trans* retinoic-acid (40 mg/m^2/day, 84 days), interferon-alpha (6x10^6 UI/day, 84 days *s.c.*) and cisplatin (40 mg/m^2/day, day 1, 28 and 56, *i.v.*) (90). Seven objective responses were observed (21%), suggesting some degree of synergism between all-*trans*-retinoic acid, interferon-alpha and cisplatin.

A randomized study compared 5-FU alone with 5-FU plus mitomycin-C in patients with advanced oesophago-gastric cancer (91). A total of 254 patients with adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma involving the oesophagus, oesophago-gastric junction or the stomach were randomized. The overall response rate was 16.1% in patients treated with 5-FU alone compared with 19.1% for those treated with 5-FU plus MMC (p=0.555) with a median survival of 6.3 months for 5-FU *versus* 5.3 months for the combination (p=1.0). Toxicity was mild for both treatments. Symptomatic benefit measured by improvement in pain control, weight loss, dysphagia, esophageal reflux and quality of life scores were comparable in each arm.

The aim of a study conducted by Morgan-Meadows and colleagues was to evaluate the overall response rate, toxicity and overall survival in thirty-five patients with advanced esophageal cancer treated with gemcitabine, 5-FU and leucovorin (92). Treatment cycles consisted of infusions of gemcitabine 1,000 mg/m^2, leucovorin 25 mg/m^2 and 5-FU 600 mg/m^2, all at days 1, 8 and 15, repeated every 28 days. One complete response and ten partial responses were observed for an overall response rate of 31.4%. An additional 11 patients had stable disease. The median survival was 9.8 months with a 1-year survival rate of 37.1%. Toxicity was predominately hematological, with 58% of patients experiencing grade 3 or 4 neutropenia.

Combination with irinotecan. The combination of irinotecan and cisplatin was evaluated in a phase II study by Ilson *et al.* as first line chemotherapy in metastatic adenocarcinoma (23 patients) and squamous cell carcinoma (12 patients) of the esophagus (93). Major objective response was observed in 57% of patients. Similar responses were observed for adenocarcinoma (52%) and squamous cell carcinoma (66%), with a median survival of 14.6 months. Toxicity, except neutropenia and diarrhea, was mild.

Another combination was evaluated by Govindan *et al.* (94). Patients received irinotecan at 160 mg/m^2 over 90 minutes followed by docetaxel at 60 mg/m^2, both repeated every 21 days. Only 10 were evaluable for response and survival. This combination resulted in a response rate of 30%; an additional 40% achieved stable disease. The median survival was 130 days. The toxicities included 71% incidence of grade 4 hematological toxicities, with 43% febrile neutropenia.

Lordick and colleagues assessed the toxicity and efficacy of the same combination in cisplatin-pretreated esophageal cancer (95). Irinotecan 160 mg/m^2 plus docetaxel 65 mg/m^2 once every 3 weeks led to severe myelosuppression in four patients, all of whom experienced neutropenic fever. After amendment, 24 patients with advanced esophageal cancer received irinotecan 55 mg/m^2 plus docetaxel 25 mg/m^2 on days 1, 8 and 15 every 4 weeks. Response rate was low at 12.5% and the median survival time was 26 weeks.

Conclusion

A large number of phase II and III studies published since the end of the 1970s have been identified and evaluated in this review. Many of these regimens achieve moderate response rates, some of them at the expense of increased toxicity. However, even the most intensive regimens cannot produce complete responses in more than 10% to 15% of patients, nor can they extend median survival beyond one year.

In the last few decades, much effort has been put into studies with chemotherapy alone or in combination with other modalities. Unfortunately, most of the published studies are phase II studies or underpowered phase III studies with small numbers of patients and it is impossible to state that one regimen is superior to others because of different drugs, different combinations of drugs, different endpoints and the wide range of results found using the same drugs or combinations. In addition, most trials did not distinguish between locally advanced and metastatic esophageal cancer, which might require a different therapeutic approach.

Based on data from recent phase II trials indicating the activity of new cytotoxic agents such as paclitaxel, docetaxel and irinotecan in recurrent or metastatic esophageal cancer, these agents are now being incorporated into combined-modality regimens (96-98).

When assessing the value of anticancer treatment, it is important to consider the impact on both survival and quality of life. In only 2 trials was a significant effect of chemotherapy on the quality of life and/or overall survival demonstrated (73, 99). In these two trials, patients with both esophageal and gastric cancer (predominantly adenocarcinomas) were treated.

Equally important is the development of novel agents and targeted therapies for the management of this disease. As more is understood of the details of carcinogenesis in this malignancy, new therapeutic strategies might be targeted at interrupting the various pathways that are important for the development of malignancy. These novel agents will be divided into five different categories according to the pattern of acquired capabilities of the malignant cells: (i) agents directed to interfere with self-sufficiency in growth signals, such as epidermal growth factor receptor (EGFR) inhibitors; (ii) agents directed to inhibit the angiogenesis process; (iii) agents directed to interfere with the limitless replicative potential, such as cell cycle inhibitors; (iv) agents directed to promote apoptosis, such as proteasome inhibitors; and (v) agents directed to inhibit the tissue invasion and metastasis processes, such as matrix metalloproteinases inhibitors.

In esophageal cancer, novel targeted treatments are in early development, although encouraging results have been reported with antibodies directed at the EGFR ligand, as well as oral tyrosine kinase inhibitors. Within the coming years, new, well-designed, adequately powered research trials will expand our treatment options greatly, given the wealth of potential targets and the plethora of new agents in clinical development. Future trials will include the addition of targeted agents to chemotherapy in metastatic esophageal cancer and to combined chemoradiotherapy in locally advanced disease. Moreover, future research directions must focus on tailoring therapy to specific patient populations, such as those with genetic mutations on receptors, for optimal therapeutic effect.

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