Esophageal cancer: chemotherapy as palliative therapy

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Introduction

Esophageal cancer represents the seventh leading cause of cancer death in the Western world, and more than 90% of all patients diagnosed will ultimately die as a consequence of their disease. Distant metastases are present in about half of the patients at the time of initial diagnosis. In the remaining 50% of patients, who present initially with locoregional tumors, systemic metastatic disease will develop in the large majority of them. This fatal malignant disease is increasing in incidence, with a shift in histological type from squamous cell carcinoma (SCC) to adenocarcinoma (AC). A variety of single agents and combination regimens have been evaluated in patients with recurrent or metastatic carcinoma of the esophagus since the early 1970s. The accumulated experience with chemotherapy to date is almost entirely in patients with squamous cell histology, and only recently have trials with new agents included both histologies. The few studies that have been reported in metastatic AC of the esophagus, however, indicate a similar chemosensitivity for AC and SCC.

Conventional agents and drug combinations

Numerous studies have investigated chemotherapy in metastatic or advanced nonresectable esophageal cancer [1–3]. When considering only results in untreated patients including modern response evaluation, the largest experience has been gained with cisplatin. Data from six phase II trials resulted in a cumulative response rate of 20% in 161 patients (95% confidence interval 14% to 26%). The duration of responses was short, and median survival generally did not exceed 7 months. A number of other ‘conventional’ anticancer drugs were shown to induce objective tumor remissions in at least 15% of untreated patients with measurable disease. Although the number of treated patients is limited, vindesine, vinorelbine, bleomycin, etoposide and 5-fluorouracil (5-FU) ± biochemical modulators such as leucovorin or interferon-α may be regarded as active at least in SCC of the esophagus (since most of the older trials were restricted to this histological subtype).

The first generation of combination protocols was based on regimens containing cisplatin/bleomycin or cisplatin/methotrexate in two-, three-, or four-drug schedules. The results of these trials were published between 1981 and 1988. Remission rates of 30% were usually achieved in patients with metastatic or locally advanced SCC, with short-lasting responses and median survival times of 6–8 months. In view of the increased toxicity associated with the first-generation protocols, there was obviously no advantage compared with single-agent treatment. In the late 1980s, cisplatin/5-FU combinations raised increasing interest in esophageal cancer because of their potential drug synergy. Until today, the classical dose schedule of this two-drug combination [cisplatin 100 mg/m² day 1 and 5-FU 1000 mg/m²/day continuous infusion (CI) for 96–120 h] is the regimen most commonly used to treat patients with either SCC or AC histology. A 35% response rate has been observed in patients with metastatic, recurrent or locally advanced nonresectable SCC of the esophagus [4, 5]. Higher response rates (in the range of 40 to 60%) have been reported from trials administering two to three cycles of cisplatin and 5-FU as neo-adjuvant therapy before surgery [3]. The difference in response rates may be related to better performance and nutritional status, as well as smaller volume disease in the surgical candidates. Attempts to substitute carboplatin for cisplatin have been unsuccessful [6]. Three studies using interferon-α-2a as a biomodulator of 5-FU in the cisplatin combination suggested possible benefit, but toxicity (myelosuppression, severe neurological disturbances and fatigue) was considerably increased, precluding recommendation of this approach outside of clinical trials [1]. Following promising results in gastric AC, cisplatin/etoposide-based combinations have been investigated since 1988. Response rates of 30 to 48% in AC and 48 to 52% in SCC were achieved with this combination, and median survival times of 8.5–12 months were reported [1]. These results seem well comparable with cisplatin/5-FU combinations. The toxicity profile showed no severe mucositis and diarrhea but, on the other hand, severe leukocytopenia occurred in up to 80% of the patients and alopecia was very common. Thus cisplatin/etoposide-based regimens did not show a particular advantage in comparison with cisplatin/5-FU.

Taxanes

Because paclitaxel is one of the most active single agents in esophageal cancer, evaluation of combination regimens, specifically with cisplatin±5-FU was a logical consequence. In three phase II trials of paclitaxel and cisplatin, response rates ranged from 44% to 52%, with antitumor activity being comparable in both histological types [7–9]. Ilson and co-workers [7] investigated paclitaxel administered by 24-h infusion in doses of 200–250 mg/m² with growth factor support combined with cisplatin 75 mg/m². Toxicity, primarily myelosuppression, was severe, leading to one or more
hospitalizations in half of the patient population and five treatment-related deaths; as such, this particular combination regimen cannot be recommended for further use. Van der Gaast and associates reported two separate trials [8, 9]. The first evaluated escalating doses of 3-h infusion paclitaxel (100–200 mg/m²) combined with a fixed dose of cisplatin (60 mg/m²²) administered every 2 weeks. A 52% response rate was observed in 59 patients. Drug doses above 180 mg/m² caused dose-limiting neurotoxicity. The second phase I trial evaluated a weekly 3-h paclitaxel and cisplatin (70 mg/m²²) infusional regimen. A preliminary report indicated that the maximum tolerated dose of paclitaxel was 100 mg/m²²/week, and that the response rate was 50% among 22 adenocarcinoma patients.

The three-drug combination of paclitaxel (3-h infusion period to reduce myelosuppression), combined with cisplatin and CI 5-FU (with both drugs given on days 1–5) was evaluated in 60 patients in a multicenter trial [10]. A 48% overall (complete plus partial) response rate was reported with significantly more complete responses (CRs) in patients with squamous cell histology. Toxicity was severe with 48% of patients requiring dose attenuation, and half of the patients were hospitalized, primarily for stomatitis and febrile neutropenia. The addition of paclitaxel to the established cisplatin/5-FU regimen did not raise the response activity sufficiently to warrant further evaluation in a larger comparative trial.

Docetaxel, a semi-synthetic taxoid developed in the 1980s, has also been investigated as monotherapy and in combination with cisplatin in patients with advanced gastroesophageal cancer. In an Eastern Cooperative Oncology Group study of gastric cancer, eight esophageal AC patients were included and treated with docetaxel alone every 3 weeks [11]; two of them responded (25%). In an Austrian phase II study, an every two weeks combination regimen consisting of docetaxel 50 mg/m² and cisplatin 50 mg/m² both given on day 1 was investigated in 37 patients with metastatic gastroesophageal cancer [12]; 13 patients with esophageal AC were included in this study population. To counteract myelosuppression, which was likely to represent the dose-limiting toxicity, a 5-day course of granulocyte colony-stimulating factor was used if the neutrophil counts on the day of scheduled chemotherapeutic drug administration were 1000–2000/µl. An encouraging confirmed response rate of 46% (including 11% CRs), a median time to progression of 7 months and a median overall survival of 11.5 months were reported. Grade 4 neutropenia occurred in only three patients, and also non-hematological side-effects were usually mild to moderate.

**Irinotecan**

The topoisomerase inhibitor irinotecan has recently shown promising activity in a number of gastrointestinal malignancies, including gastric and esophageal cancer. When used as a single agent with a weekly dose of 125 mg/m², a response rate of 15% was documented in two recent phase II trials [13, 14]. The combination of weekly irinotecan and weekly 5-FU/leucovorin, a regimen commonly used in colorectal cancer in the USA, has resulted in a modest response rate of 22% in a total of 113 patients treated in two phase II trials [15, 16]. Based on *in vitro* evidence of a sequence-dependent synergy, a phase II trial evaluated a combination regimen consisting of irinotecan 65 mg/m² and cisplatin 30 mg/m² given weekly for 4 weeks, followed by a 2-week rest period [17]. An overall response rate of 57% was observed in 35 patients, with comparable responses seen in AC and SCC. Dysphagia and global quality-of-life were improved in the majority of patients. Therapy was fairly well tolerated except for myelosuppression, which led to treatment delays or early discontinuation in almost two-thirds of patients. A confirmatory trial in gastric and gastroesophageal cancer using the same regimen also yielded a response rate of 54%; because of the common occurrence of myelosuppression and diarrhea, a dose reduction of irinotecan to 50 mg/m² in previously treated patients was recommended [18]. In an attempt to improve delivery of therapy and ameliorate hematological toxicity, a national multicenter trial has subsequently investigated the above-mentioned weekly irinotecan and cisplatin doses delivered on a ‘2 weeks on’ and ‘1 week off’ schedule [19]. With this modified regimen, confirmed partial responses were noted in 10/28 (36%) assessable patients. As anticipated, the tolerance of treatment was improved with 22% of patients experiencing grade 3/4 neutropenia, 19% had grade 3 diarrhea 8% grade 3 nausea and 14% grade 4 fatigue.

In a randomized phase II trial involving 148 patients with advanced gastric or gastro esophageal junction adenocarcinoma, a different irinotecan (200 mg/m² day 1) plus cisplatin (60 mg/m² day 1 every 3 weeks) regimen was compared with irinotecan (80 mg/m²) plus leucovorin (500 mg/m²) and CI 5-FU (2000 mg/m² over 22 h weekly for 6 weeks and 1-week rest). Both combinations were described as active and fairly well tolerated; based on the overall confirmed response rate among the first 63 assessable patients (28% versus 42%) however, the irinotecan/CI 5-FU/leucovorin arm was selected for further phase III investigation [20].

Optimal dose regimens for other irinotecan-based combinations such as irinotecan plus docetaxel remain to be defined because of an unexpected high rate of severe adverse reactions noted in early phase II studies [21, 22]. Only rather low and fractionated doses of this potential synergic drug combination seem to result in an acceptable therapeutic index, as shown in a recent phase II study reported by Burtness and co-workers [23].

**Oxaliplatin**

Oxaliplatin is a novel antineoplastic platinum analog with a potentially more favorable toxicity profile than cisplatin [24]. At clinically effective doses, it is less emetic, less nephrotoxic and less neurotoxic than cisplatin. Following the successful introduction of oxaliplatin into the therapeutic management of colorectal cancer, its clinical utility is currently being investigated in a variety of other malignancies, including cancers of the upper gastrointestinal tract. A National Cancer Institute
sponsored phase I/II clinical trial using oxaliplatin combined with protracted-infusion 5-FU plus radiotherapy for patients with primary esophageal cancer, stages II–IV, has recently been reported [25]. Cycle 1 consisted of oxaliplatin 85 mg/m² on days 1, 15 and 29; CI 5-FU 180 mg/m²/24 h was given 35 days, and radiotherapy 1.8 Gy in 28 fractions starting on day 8. At completion of cycle 1, stage IV patients were scheduled to continue therapy in the absence of disease progression; 38 eligible patients with a primary tumor endoscopically assessable for response, including 22 non-invasively stage IV patients, were entered in this study. The combined modality therapy was well tolerated, although drug doses could not be escalated due to dose-limiting toxic effects. After cycle 1, 29 patients (81%) had no cancer detectable in the esophageal mucosa. Out of the 16 stage II/III patients, 13 underwent surgery, and five patients (38%) exhibited pathological CRs. In another phase II study, the antitumor activity of a twice a month regimen of oxaliplatin (85 mg/m² on day 1), leucovorin (500 mg/m² days 1 and 2) and 5-FU (400 mg/m² bolus followed by 600 mg/m² as 22 h CI days 1 and 2) was examined [26]; 34 patients with metastatic carcinoma of the esophagus or gastric cardia were enrolled. After a median follow-up of 6 months, 14/29 (48%) assessable patients had an objective response, including one CR. The regimen was described to be well tolerated, with the predominant toxicity being neutropenia.

**Gemcitabine**

In view of the need to identify new active agents in esophageal cancer, gemcitabine, a deoxycytidine analog, had also been investigated in various solid tumors. Kropotkine and co-workers have extended their phase I/II experiences [27]: 36 patients with unresectable or metastatic esophageal adenocarcinoma or SCC were treated with gemcitabine 800 mg/m² on days 2 and 9 and 16 every 4 weeks. Toxicity was substantial and tended to be cumulative. The most frequent grade ≥3 toxic effects were neutropenia (83%), thrombocytopenia (67%) and anemia requiring treatment with erythropoietin, red blood cells or both (81%). Non-hematological adverse reactions were mild to moderate and consisted mainly of nausea/vomiting and fatigue. Fourteen out of 34 assessable patients (41%) had an objective response, and the median actuarial survival was 9.8 months.

Another gemcitabine combination regimen with a preclinical rationale indicating dose-dependent synergy, i.e. gemcitabine (1000 mg/m²) + irinotecan (100–115 mg/m²) both administered on days 1 and 8 every 3 weeks, was investigated in 61 patients with advanced stage disease [28]. The primary grade 3/4 toxic events included diarrhea, dehydration and myelosuppression, and there have been four treatment-related deaths. The poor tolerance contrasts with a modest therapeutic effectiveness of only 55% of the patients still alive after 6 months.

**In summary**, more recent trials of combination regimens that have included the taxanes, irinotecan or oxaliplatin appear to have higher response rates than previous regimens; however, duration of response typically lasts no longer than a few months, and survival in advanced stage disease remains short, rarely exceeding 1 year. Some of the new drug combination trials have been reported only in preliminary abstract form and consist of small numbers of assessable patients. In addition, the toxic effects associated with many of these phase II single institutional experiences have been excessive. Further follow-up of early reports and additional patient trials using the most promising and tolerable dose regimens are therefore needed. Although many oncologists continue to promote multi-agent chemotherapy (with cisplatin and infusional 5-FU representing the reference first-line treatment of patients with recurrent or metastatic disease of either histology), some continue to use serial single agents. Objective analysis of available data, in fact, suggests that no single regimen seems to be so advantageous in either activity or toxicity profile as to deserve designation as the standard therapy in advanced esophageal cancer. The choice of treatment should thus be individualized on the basis of performance score and patient/physician preference.

**Prognostic factors**

Prognostic factors for survival, which may also influence the treatment decision have been well defined in a recent multivariate analysis of the baseline characteristics of 350 patients with advanced esophageal cancer who were treated in six consecutive prospective trials with cisplatin-based combination chemotherapy [29]. The main prognostic factors were found to be WHO performance status (0 or 1 versus 2), lactate dehydrogenase (normal versus elevated), extent of disease (limited, i.e. locoregional irresectable disease versus extensively disseminated disease) and the type of treatment (weekly or an every two weeks cisplatin/paclitaxel regimen versus 4-weekly cisplatin/etoposide ± 5-FU). The median survival for patients without any risk factors was 12 months, compared with only 4 months in those with WHO performance status 2 plus elevated lactate dehydrogenase and extensive disease. Two of the above-mentioned clinical predictive factors were also confirmed in a retrospective study of 126 esophageal cancer patients who were treated at the Uppsala University Hospital in Sweden between 1990 and 2000 [30]. Performance status and stage of disease were found as independent significant prognostic factors in the multivariate analysis (both with P values <0.001).

**Future directions**

Trials of conventional and novel chemotherapeutic agents in metastatic disease will continue to define the optimal dose, schedule, and combination of these agents. Still, it is becoming increasingly clear to clinical investigators that we have probably reached the limit of benefit that can be achieved
with conventional cytotoxic therapy. Areas of ongoing clinical research that may offer promise for the future include the identification of molecular markers in tumors that may predict response or resistance to chemotherapy [2, 24] and the new molecular tumor-targeted therapies such as agents affecting growth factor receptor pathways, tyrosine kinase inhibitors, and agents that may inhibit angiogenesis, invasion and metastasis [31]. Also of interest is the alternative assessment of response to chemotherapy using metabolic imaging, such as positron emission tomography [2, 32].

References