Triple Induction Chemotherapy and Chemoradiotherapy for Locally Advanced Esophageal Cancer. A Phase II Study

WOLFGANG EISTERER 1, ALEXANDER DE VRIES 2, DOROTA KENDLER 3, BERNHARD SPECHTENHAUSER 4, ALFRED KÖNIGSRAINER 5, HERMANN NEHODA 6,8, IRENE VIRGOLINI 3, PETER LUKAS 7, OLIVER BECHTER 1, EWALD WÖLL 9 and DIETMAR ÖFNER 10

1 Department of Internal Medicine I, Innsbruck Medical University, Innsbruck, Austria; 2 Department of Radio-Oncology, Feldkirch General Hospital, Feldkirch, Austria; 3 Division of Nuclear Medicine, Innsbruck Medical University, Innsbruck, Austria; 4 Department of Surgery, Kufstein General Hospital, Kufstein, Austria; 5 Department of General, Visceral and Transplant Surgery, University of Tübingen, Tübingen, Germany; 6 Department of Surgery, St. Johann General Hospital, St. Johann, Austria; 7 Division of Radio-Oncology, Innsbruck Medical University, Innsbruck, Austria; 8 Division of General and Transplant Surgery, Innsbruck Medical University, Innsbruck, Austria; 9 Department of Internal Medicine, St. Vincent Zams General Hospital, Zams, Austria; 10 Department of Surgery, Paracelsus Medical University Salzburg, Salzburg, Austria

Abstract. Background: This phase II trial assessed the feasibility and safety of induction chemotherapy with cisplatin (25 mg/m² d1-5, d29-34)/docetaxel (75 mg/m² d1, d29)/5-fluorouracil (5-FU, 750 mg/m² d1-5, d 29-34) followed by external beam radiotherapy concurrent with docetaxel (15 mg/m² d1,8,15,22) and 5-FU (300 mg/m² continuous infusion on the days of radiotherapy). Patients and Methods: Twenty-four patients with locally advanced carcinoma of the esophagus were included. Following chemotherapy and chemoradiation eligible patients underwent esophagectomy. If surgery could not be performed patients received definitive radiation. Results: Sixteen patients underwent resection. Pathologic complete remission was achieved in 5 of those 16 patients, 13 patients had downstaging of disease. R0 resection was feasible in all 16 patients. Main grade 3 and 4 toxicities were neutropenia in 10 patients, diarrhea in 4 and postoperative morbidity in 9 patients. At a median follow-up of 16.5 months 15 patients are alive; median survival has not yet been reached. Conclusion: Neoadjuvant treatment with cisplatin/docetaxel/5-fluorouracil followed by chemoradiation with docetaxel/5-fluorouracil is safe, feasible, and effective. Main toxicities are neutropenia and postoperative morbidity. Esophageal cancer is the sixth leading cause of cancer death worldwide and its mortality rate nearly reaches its incidence rate (1). Surgery remains the standard treatment for patients with resectable esophageal cancer, but the long-term prognosis is unsatisfactory, with an overall 5-year survival rate ranging from 15-22% (2). The poor outcome for this type of cancer is due to the systemic nature of the disease which is reflected by lymph node metastasis occurring early in the course of the disease.

Adding chemotherapy and radiotherapy to the management of locally advanced esophageal cancer has been evaluated in numerous phase II trials (3). Neoadjuvant chemoradiation (CRT) seems to be beneficial in patients who achieve a complete pathological response (pCR). A phase III study of combined radiochemotherapy versus radiotherapy alone reported a superior 5-year survival for the combination therapy (4, 5). A recent meta-analysis concluded that preoperative chemoradiation leads to a significant survival benefit (6).

Docetaxel is an active agent for the treatment of upper gastrointestinal cancer (7-10). Due to the inhibitory effect on the cell cycle in the G2/M-phase, the drug also has radiosensitizing properties (11). Docetaxel in combination with hyperfractionated radiotherapy led to 44% pCR in esophageal cancer, with moderate side-effects (12). Triple induction therapy with two cycles of induction chemotherapy followed by CRT with paclitaxel, another taxane, has been shown to induce adequate pCR of 30% and a high rate of R0 resection (13).

The present study is a prospective phase II trial investigating a triple induction chemotherapy with docetaxel,
cisplatin, 5-fluorouracil (5-FU) for two cycles followed by external beam radiotherapy concurrent with docetaxel (once per week, four times) and continuous infusional 5-FU in patients with locally advanced esophageal adenocarcinoma (AC) or squamous cell carcinoma (SCC). The primary endpoint of the study is, to discover the feasibility and safety of this treatment strategy. Secondary endpoints are, to determine the rate of downstaging, the pCR rate, the toxicity, the rate of local and systemic recurrence and the median overall survival.

Patients and Methods

Eligibility and pretreatment evaluation. All patients included in the study were evaluated by an experienced multidisciplinary team consisting of medical oncologists, radiation oncologists, radiologists and oncologic surgeons. Eligibility criteria were age >18 and <75 years, histologically proven and previously untreated SCC or AC of the esophagus, WHO performance status (PS) ≤2, absolute neutrophil count ≥1.5×10⁶/l, platelet count ≥100×10⁶/l, adequate renal and hepatic function. Only patients with potentially resectable disease were entered into the study. All patients were required to give written informed consent. The study was approved by the local Ethics Committee (AN1735).

Pretreatment evaluation included patients’ medical history, physical examination, complete blood cell count, serum chemistry, barium esophagram, esophagoscopy including endoscopic ultrasound (EUS), computed tomographic (CT) scans of the chest and abdomen, 18-fluorodeoxyglucose positron-emission-tomography (FDG-PET) prior to treatment and after chemoradiation.

Patients were assigned a preoperative clinical stage according to EUS results based on the 1997 TNM classification of the International Union Against Cancer (14).

Treatment. Therapy consisted of docetaxel at 75 mg/m², given as a 1 h infusion on days 1 and 29; cisplatin at 15 mg/m² given on days 1-5 and 29-33 over 30 min; and 5-FU at 750 mg/m² on days 1-5 and 29-33 given as a continuous infusion using a mechanical pump device. Patients were prehydrated before the application of cisplatin with 1000 ml of 0.9% saline; after cisplatin an additional 1000 ml of 0.9% saline was given. To facilitate diuresis, 40 mg of furosemide were administered. All infusions were given via an implantable port-system.

Supportive care including antiemetic therapy, nutritional support and blood transfusions were allowed according to the treating physician following good clinical practise (GCP) guidelines. The routine use of growth factors was not permitted.

Radiotherapy was delivered in a three-dimensional conformal mode based on a total of 40 or 60 Gy given in 20 or 30 fractions over 4–6 weeks. Concomitant chemotherapy comprised 5-FU at 300 mg/m² continuous infusion on the days of radiotherapy and docetaxel at 15 mg/m² on days 1, 8, 15, and 22 of radiation therapy. The dosage for individual patients was governed by the dose constraints of normal organs. The radiotherapy was delivered in two or three consecutive phases. Phase I started with anterior-posterior opposing portals to 30 Gy, while phase II was given with three fields to another 10 Gy. If the patient was unable to undergo surgery e.g. because of general condition, in phase III, another 20 Gy to the tumor region was given, regarding limiting radiation dose to the heart, lung, and spinal cord. The target volume (TV) included the site of the primary and pathological lymph nodes assessed on planning CT scan and esophagoscopy. Nodes were defined as positive if the diameter was 1 cm or more on at least one CT scan slice.

Tumor resection with extended en bloc lymphadenectomy was performed in operable patients within four weeks after termination of radiochemotherapy. In the case of inoperability, radiotherapy alone up to 59.6 Gy was applied without concomitant chemotherapy.

Response and toxicity evaluation. Tumor assessment after two cycles of DCF included physical examination, nutritional status, weekly blood cell count, renal and liver function tests every four weeks and CT of the thorax and the abdomen to exclude progressive disease. After completion of chemoradiation (week 14) CT scan, 18-fluorodeoxyglucose positron-emission-tomography and EUS were repeated. Toxicity was graded according to the NCI-CTC version 2.0 (15). All recorded events during the treatment period were considered toxic. Tumor assessment was made according to RECIST 1.1 criteria (16).

Statistical analysis. The primary study endpoint of the trial was the evaluation of safety and feasibility, as well as objective tumor response, of a triple induction chemotherapy protocol followed by chemoradiation for patients with potentially resectable esophageal cancer. Sample size was determined by Gehan-design (17) assuming that a response rate of 40% or less was considered insufficient to pursue further investigation. The design minimizes the expected number of treated patients in case of inadequate response. If no responder was detected in the first 14 treated patients, the study would have been closed. In case of one or more responding patients, additional patients could be included in the protocol up to a predetermined number of 24 patients in total. Secondary endpoints were toxicity, complete pathological response and survival. Survival time was calculated from the beginning of chemotherapy to the date of death, or last follow-up according the Kaplan-Meier method. Analyses were performed using the SPSS statistical software package (©2010, SPSS Inc., Stanford, CA, USA).

Results

Patient characteristics. A total of 24 patients from two cancer centres were enrolled in the study between October 2003 and 2006. The median age was 58.5 years (range, 33-74 years), 2 patients were female, 16 had SCC and 8 AC. Patient characteristics and pretreatment diagnostic tests are shown in Table I. A total of 66 cycles of chemotherapy and chemoradiation were administered (3 per patient). Median dose intensity for cisplatin, 5-FU, and docetaxel were 98%, 100%, and 97% respectively. Dose reductions were necessary in two patients due to non-hematological toxicity.

Treatment outcomes. Accrual and treatment summary are depicted in Figure 1. Two patients went off protocol during induction of chemotherapy. Two patients received a feeding tube during neoadjuvant therapy. No patient showed disease progression radiographically after the end of the induction chemotherapy. Twenty-two patients completed chemoradiation and were evaluated for response, toxicity and survival. Six
patients did not undergo surgery and received definitive radiotherapy up to 59.6 Gy according to the protocol. Four patients were judged unfit for general anesthesia and in two cases, the tumor was not expected to be R0 resectable, although no disease progression occurred during neoadjuvant treatment. The surgical outcomes are listed in Table II. Sixteen patients underwent resection; pCR was achieved in 5 out of these 16 patients. An additional three patients were assessed as having ypT1N0 (scattered viable tumor cells present) stage at resection. Downstaging of the disease was achieved in 13 patients. R0 resection was possible in all patients who underwent surgery. Six patients exhibited postoperative morbidity; two with anastomotic stenosis, two with anastomotic insufficiency, one with fistula and one with nervus recurrens palsy. There was one postoperative death 39 days after resection due to a fatal bleeding at the anastomotic site. We recorded six systemic recurrences and one patient with both local and systemic relapse. Seven patients died during follow-up (five due to progressive disease, one due to fatal bleeding at the anastomotic site and one due to a non medical condition). Four out of these seven patients were who had undergone resection, three had undergone definitive radiotherapy. At a median follow-up of 16.5 months, 15 patients are alive, median survival has not yet been reached. All patients with documented pCR are alive at 13-45 months of follow-up.

### Toxicity and dose intensity
The toxicity profile of neoadjuvant chemotherapy and chemoradiation is listed in Table III. Induction chemotherapy with docetaxel, cisplatin, and 5-FU was well tolerated. Main grade 3/4 toxicities were the following: leucopenia in 10/24 patients, diarrhea in 4 patients, alopecia in 2 patients; other grade 3 or 4 toxicity occurred in 5/24 patients including deep vein thrombosis, blurred vision, fever, pulmonary embolus, and arterial hypertension (Table III). Two patients had to be taken off protocol, one due to psychological catatonia after the first course of chemotherapy, and the other due to a protocol violation after the second course of chemotherapy. Dose reductions were necessary in two patients due to non-hematological toxicity (diarrhea, arterial hypertension). The median dose intensity during induction chemotherapy was 97% for docetaxel, 98% for cisplatin, and 100% for 5-FU. Chemotherapy was administered according to the treatment schedule to all patients.

The most frequent toxic effect during chemoradiation was esophagitis grade 1 and 2 in 14 out of the 22 evaluable patients (Table IV); grade 3 esophagitis was observed in only one patient. Other commonly experienced toxicities were grade 1 anemia in 11 patients and treatment field erythema grade 1 in 10 patients. No grade 4 toxicity was observed during chemoradiation. None of the patients developed radiation-induced pneumonitis.

**18FDG-PET scan.** Pre- and post-treatment 18FDG-PET scans were available for 16 patients. The mean maximum standard uptake value (SUV) of the primary tumor before therapy was 14.3 (range: 6.6-54.2). After completion of chemoradiation,
this value decreased to a mean of 5.0 (range: 3.7-12.0). The mean decrease of maximum SUV following treatment was 7.8 (range: 2.6-46.7). SUV decrease did not differ between SCC and AC. SUV decrease did not predict for pathological response in patients who had undergone resection. All patients with an SUV decrease greater than 10 (n=6) were still alive at the last follow-up (range: 13-46 months); in contrast, 3 out of 10 patients with an SUV decrease less than 10 died.

Discussion

The treatment of localized esophageal cancer is a matter of controversy. The standard of care is surgical resection. However, long-term survival is poor, with 5-year survival rates ranging from 15%-22% (2). This failure of a sole surgical approach is attributable to the systemic nature of the disease, which often leads to a systemic relapse after curative...
resection. Adjuvant or neoadjuvant systemic therapy was added to surgery in order to increase curability, however, this has yielded conflicting results. Three major phase III trials (18-20) demonstrated that preoperative chemotherapy can be administered to the majority of patients with esophagogastric cancer, while fewer than half receive their assigned postoperative adjuvant chemotherapy. Therefore the role of adjuvant therapy remains unclear (21). The potential of neoadjuvant therapy to increase curability is likely not to be fully developed yet, since up to date the most frequently used drugs are cisplatin and 5-FU-based chemotherapy protocols. Despite Cisplatin being the most frequently used radiosensitizing drug, better results might be achieved by using more effective, modern drug combinations and modern radiation planning. A more recent study of smaller scale pursued the concept of induction triple therapy including taxanes and radiochemotherapy, showing that this strategy is considerably active in esophageal cancer, with pCR rates of 30% and overall survival exceeding 36 months (13).

In our study, we decided to integrate a new chemotherapeutic agent, docetaxel, with well-known activity in upper gastrointestinal cancer (7-10) and excellent radiosensitizing characteristics (22) into a three-step strategy of induction chemotherapy followed by chemoradiation and surgery in patients with resectable disease. We aimed for increased efficacy of systemic therapy in order to counteract the systemic spread of the disease by using two cycles of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil. Radiochemotherapy with docetaxel was applied in order to achieve local control.

Our treatment regimen showed a good tolerability, as demonstrated by the high median dose intensities, which were above 97% for all chemotherapeutic agents used. No delay in the treatment schedule was necessary. Patients initially symptomatic from their disease exhibited a rapid and marked improvement of their condition after one cycle of chemotherapy.

The main toxicities observed were leucopenia and diarrhea. However, we did not observe leucopenic fever, although no prophylactic growth factor support was mandated by the protocol. The three-step strategy with docetaxel, cisplatin, and 5-fluorouracil chemotherapy showed a promising clinical activity with pCR rate of 31%, downstaging in 81% of the patients and R0 resection for all patients. The surgical morbidity and mortality rate, observed in our trial is comparable to the data reported in previous studies (18, 19, 23). The pCR rate of 31%, in our study, nearly matches a larger phase II study of the Swiss Group for Clinical Cancer Research employing a similar approach with cisplatin in combination with docetaxel followed by chemoradiation with both cytostatics. In their study, Ruhstaller et al. (23), recorded a pCR rate of 26% and excellent survival outcome.

Metabolic imaging by 18FDG-PET was incorporated into the initial diagnostic work-up. Re-evaluation after chemoradiation showed a decreased standard uptake value for all patients but did not predict for a subsequent response or survival benefit. This is in contrast to a recently published report by Ott et al. (24), where the authors stated that changes in tumor metabolic activity during chemotherapy predict response, prognosis and recurrence of the disease. The different results might be explained by the fact that Ott et al. used PET imaging at a much earlier time-point (14 days after chemotherapy initiation) than we did in our trial, and that adenocarcinoma patients’ images only were evaluated. Despite the controversial data, we consider PET imaging to be an integral part of the primary staging procedure due to its sensitivity at detecting occult metastatic disease (24, 25).

Six out of seven relapses observed were systemic in nature, suggesting that the triple induction approach with docetaxel, cisplatin, and 5-FU and radiotherapy with docetaxel and 5-FU achieved excellent local control, leaving systemic spread as the main threat for long-term prognosis. Systemic therapy might still be improved by increasing its dose intensity. An alternative to changing the dose intensity is to add a biological agent such as an epidermal growth factor receptor-inhibitor to the chemotherapy.

In conclusion, triple induction chemotherapy and chemoradiation with docetaxel, cisplatin, and 5-FU is safe, feasible, and effective, achieving downstaging in 81% and R0 in the majority of patients.

Acknowledgements

The Authors acknowledge financial and logistic support of the Verein für Tumorforschung Innsbruck.

References


