Phase I Study of Definitive Radio-chemotherapy with Cisplatin, 5-Fluorouracil and Cetuximab for Unresectable Locally Advanced Esophageal Cancer

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Abstract. Background/Aim: Prognoses of patients receiving radio-chemotherapy with 5-fluorouracil (5-FU) and cisplatin for unresectable esophageal cancer may be improved with the addition of cetuximab. This phase I study aimed to define the maximum tolerated dose of 5-FU when combined with cisplatin, cetuximab and radiotherapy. Treatment included 59.4 Gy of radiotherapy concurrently with two courses of cisplatin (20 mg/m², d1-4) and 5-FU (dose level 0: 500 mg/m², d1-4; dose level 1: 750 mg/m², d1-4; dose level 2: 1,000 mg/m², d1-4), followed by two courses of chemotherapy. Cetuximab was given for 14 weeks (400 mg/m² loading dose followed by 250 mg/m² weekly). Results: At dose level 1 (n=3) and 2 (n=3), no patient experienced a dose-limiting toxicity. Minor treatment modifications were due to organization or request by physicians/patients. At dose level 2, only five grade 3 adverse events occurred. Conclusion: Dose level 2 appears safe and is used in a subsequent randomized phase II study.

Esophageal cancer is considered a highly aggressive malignancy generally associated with a poor survival prognosis. It represents the sixth most common cause of cancer-related deaths worldwide (1, 2). Due to advances in surgical techniques and multi-modality treatments, the prognosis of non-metastatic esophageal cancer has slowly improved over the past decades (3, 4). However, the overall 5-year survival probability is still poor and needs to be considerably improved (5). This is particularly true for patients with locally advanced unresectable disease. Many of these patients receive definitive radio-chemotherapy, mostly consisting of cisplatin and 5-fluorouracil (5-FU) (6-9). It is questionable whether intensification of the systemic treatment could improve the outcome of these patients. Cetuximab, a monoclonal epidermal growth factor receptor (EGFR) antibody, has shown considerable efficacy when combined with radiotherapy in patients with head-and-neck cancer (10, 11). It appears likely that the addition of cetuximab to radio-chemotherapy could improve the prognosis also of patients with locally advanced esophageal cancer. However, the optimal regimen of radio-chemotherapy and cetuximab still needs to be defined. The aim of this study was to identify the maximum tolerated dose of 5-FU in combination with radiotherapy, cisplatin and cetuximab.

Materials and Methods

Patients were included in this phase I study between 2008 and 2009 after giving their written informed consent and received definitive radio-chemotherapy for unresectable locally advanced esophageal cancer. The study protocol was approved by the ethics committee of the University of Lübeck. Irradiation was performed as three-dimensional conformal radiotherapy with 6-18 MV photons following computed tomography-based treatment planning. Initially, 50.4 Gy were administered to the primary tumor and the regional lymph nodes with daily doses of 1.8 Gy given on five consecutive days per week, followed by a boost dose of 9 Gy with the same fractionation to the primary tumor and involved lymph nodes. Concurrently with radiotherapy, two courses of cisplatin (intravenous bolus of 20 mg/m² on days 1-4) and 5-FU (different dose levels as continuous infusion over 96 hours on days 1-4) were administered, followed by another two courses of chemotherapy without concurrent irradiation. In addition to this radio-chemotherapy program, weekly cetuximab was given for a total of 14 weeks. A loading dose of 400 mg/m² administered one week prior to radiotherapy was followed by 13 weekly doses of 250 mg/m². The flow chart of the study design is shown in Figure 1. Dose-limiting toxicities (DLTs), which were defined as any grade >3 toxicity, dose reduction of chemotherapy or radiotherapy by

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>30% or interruption of the treatment for longer than 14 days, were
assessed from the start of radiotherapy until 10 days following its
scheduled completion (Table I). Skin toxicity and allergic or
hypersensitivity reactions related to cetuximab were not regarded as
dLTs. A full safety evaluation was performed for all patients treated
at dose level 1, before any patient could be enrolled at dose level 2.

Three dose levels were available for the administration of 5-FU,
namely dose level 1 (750 mg/m²/day on days 1-4), dose level 2
(1,000 mg/m²/day on days 1-4) and dose level 0 (500 mg/m²/day on
days 1-4). The traditional 3+3 design was applied to specify the safe
dose of 5-FU for a subsequent study. Initially, three patients were
treated at dose level 1. If no patient experienced a DLT, the next
three patients would have been treated at dose level 2. In case of one
DLT at dose level 1, another three patients would have been treated
at this dose level. If one of six patients at dose level 1 experienced
a DLT, the next three patients would have been treated at dose level
0. No dose escalation was performed beyond level 2. If two of three
or two of six patients, respectively, at dose level 1 experienced a
DLT, the next three patients had to be treated at dose level 0. If two
of three or two of six patients, respectively, at dose level 0
experienced a DLT, the combination of radio-chemotherapy with
cisplatin and 5-FU plus cetuximab had to be considered not feasible.

Results

In the three patients treated at dose level 1 (Table II), a delay of
administration of cetuximab of more than 3 days occurred in
one patient (weeks 13 and 14), while, in one patient, the last
administration of cetuximab (week 14) was not given due to the
patient’s request. These modifications did not represent a DLT.
An interruption of radiotherapy occurred in two patients but was
not considered as a DLT. In one patient, the doses of both 5-FU
and cisplatin were reduced by 75% during course 3 due to lab
abnormality/adverse events and not given during course 4 due
to the patient’s request. In another patient, the 5-FU dose was
reduced by 25% and cisplatin was not given during course 4
due to lab abnormality/adverse events. None of these delays and
dose reductions was due to a DLT. In the three patients treated
at dose level 1, thirteen grade 3 adverse events (worst case per
patient) occurred (Table III) and four serious adverse events
(SAEs) were observed. One SAE (dysphagia) occurred during the
period of radiotherapy (day 15 since the start of treatment)
but was not related to treatment. Three serious SAEs, namely
renal toxicity, pneumonia and herpes zoster infection, occurred
following radiotherapy on days 75, 84 and 98 since the start of
treatment, respectively, and were considered definitely related,
not related and not likely related to treatment, respectively.

None of these events represented a DLT.

In consequence, the next three patients were treated at dose
level 2 (Table II). In all of these patients, a delay of the
cetuximab administration of more than 3 days was noted,
either due to lab abnormality/adverse events, patient’s request
or organizational reasons. The delay occurred in one patient
in week 13 (for 10 days), in one patient in week 4 (for 13
days) and in one patient in weeks 7, 9 and 10 (for 7, 7 and 4
days, respectively). Furthermore, in one patient the cetuximab
administration in week 3 was reduced by 20%. An interruption
of radiotherapy occurred in two patients but was not regarded
as DLT. In one patient, the dose of cisplatin was reduced by
25% during course 2 (due to lab abnormality/adverse events),
while the dose of 5-FU was reduced by 25% during course 3
(patient’s request). In the same patient, courses 2 to 4 were
delayed by 14 days. As in dose level 1, none of the delays and
dose reductions was caused by a DLT. In the three patients
treated at dose level 2, five grade 3 adverse events (worst case
per patient) occurred (Table IV), whereas two patients
experienced a SAE. One SAE (pleuritis) occurred during the
period of radiotherapy (day 28 since start of treatment) but
was not related to treatment. The other SAE, infection,
occurred on day 84 and was considered probably related to
treatment. Both events did not represent a DLT.
At dose level 1, best response was stable disease in one patient, partial response in one patient and complete response in one patient, respectively. At dose level 2, one patient had systemic progression with locally controlled disease, one patient stable disease and one patient partial response, respectively.

**Discussion**

The optimal treatment of locally advanced esophageal cancer is controversial (12-15). The decisions with respect to appropriate treatment approach are often made on an individualized basis taking into account several factors, including the patient’s age, general condition and comorbidities. According to a retrospective study of 148 patients, the best results for patients with locally advanced disease are achieved with neoadjuvant radio-chemotherapy plus microscopically complete (R0) resection (16). If a R0-resection appears unlikely, radio-chemotherapy should be continued and given as definitive treatment, since neoadjuvant radio-chemotherapy plus incomplete (R1/2) resection resulted in worse outcomes than definitive radio-chemotherapy alone. In this retrospective study, the 1-year survival rates were 90% after neoadjuvant radio-chemotherapy (41.4-50.4 Gy) plus R0-resection, 22% after neoadjuvant radio-chemotherapy plus R1/2-resection and 47% after definitive radio-chemotherapy (59.4-66.6 Gy), respectively (16). The 1-year rates of locoregional control were 94%, 19% and 52%, respectively.

Patients with unresectable esophageal cancer have a significantly worse prognosis than those with resectable disease and require particular attention. After publication of the results of a randomized trial in 1992, which demonstrated that radio-chemotherapy was superior to radiotherapy alone (median survival times=12.5 vs. 8.9 months, \( p<0.001 \)), radio-chemotherapy with 5-FU and cisplatin became the standard regimen for definitive treatment of esophageal cancer (7). In the 1992 trial, chemotherapy included four courses of 5-FU (1,000 mg/m\(^2\)/day on days 1-4) and cisplatin (75 mg/m\(^2\) on day 1). Two courses were administered concurrently with radiotherapy and two courses following radiotherapy. In order to achieve a better radio-sensitizing effect and decrease acute toxicity, 75 mg/m\(^2\) cisplatin given on day 1 may be replaced by 20 mg/m\(^2\) cisplatin on days 1-4 (16-20). However, the results of definitive radio-chemotherapy for esophageal cancer are still unsatisfactory.
Table III. Adverse events (worst case per patient) in patients treated at dose level 1:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster infection</td>
<td>1</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Night sweats</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
</tr>
<tr>
<td>Performance status</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
</tr>
</tbody>
</table>

Table IV. Adverse events (worst case per patient) in patients treated at dose level 2:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
</tr>
<tr>
<td>Exanthema</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
</tr>
</tbody>
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and require improvement. Escalation of the radiation dose did not result in better survival rates according to the results of phase II trial (8). Improvement of the patients’ prognosis may, therefore, be achieved with intensification of the systemic treatment.

Today, new neoadjuvant radio-chemotherapy regimens are under investigation. In a phase I/II trial, radiation with docetaxel and oxaliplatin in patients with advanced cancer of the esophagogastric junction appeared safe and showed efficacy with a median overall survival of 29.5 months in patients treated at the higher dose level (21). One option would be the addition of modern targeted therapies, such as EGFR antibodies, which resulted in significantly improved outcomes in patients irradiated for head-and-neck cancers (10, 11). In a randomized phase III trial of 424 head-and-neck cancer patients, the median survival times were 49.0 months after radiotherapy plus cetuximab and 29.3 months after radiotherapy alone (p=0.018) (8). The 5-year survival rates were 46% and 36%, respectively (11). For this reason, the present phase I study investigated the feasibility of the addition of a treatment regimen that included radiotherapy, 5-FU, cisplatin and the EGFR antibody cetuximab. Similar to other studies, cetuximab was well-tolerated and caused no DLT (22, 23). A grade 1 cetuximab associated acneiform rash was observed in two patients, i.e., in one patient at each dose level. According to previous studies, such skin reactions caused by cetuximab are well manageable (10, 11, 24). In addition, a grade ≥2 acneiform rash was reported to be a marker for response to treatment with cetuximab (25). The results of the present study agree with this finding taking into account the relatively unsatisfactory response and the absence of a ≥2 acneiform rash. This may be the result of a low expression of EGFR and mutation of the K-RAS gene of the tumors investigated in this study (26). Currently it is not clear whether addition of cetuximab to the radio-chemotherapy of esophageal cancer can improve the overall survival of these patients (27, 28). In the SCOPE 1 trial, treatment included two courses of induction chemotherapy with cisplatin (60 mg/m^2 on day 1) and capcitabine (625 mg/m^2 twice daily on days 1-21) followed by radio-chemotherapy with 50 Gy of radiotherapy plus two concurrent courses of chemotherapy with or without the addition of cetuximab. In this trial, patients receiving cetuximab had a worse median survival (22.1 vs. 25.4 months, p=0.035). However, the treatment programs used in the SCOPE 1 trial for definitive treatment appeared not optimal. The radiation dose appeared relatively low and induction chemotherapy may have led to anemia and subsequent tumor hypoxia, which is known to impair the effect of radiotherapy (29). In contrast to the SCOPE 1 trial, the preliminary results of a randomized phase II study showed a better progression-free survival (PFS) in patients receiving cetuximab in addition to radio-chemotherapy (27). In this phase II study, radio-chemotherapy included 59.4 Gy of radiotherapy plus two concurrent courses of cisplatin (20 mg/m^2 on days 1-4) and 5-FU (1,000 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2 on days 1-4) followed by two additional courses of cisplatin (20 mg/m^2 on days 1-4) and 5-FU (750 mg/m^2 on days 1-4). Median times of PFS were 15.5 months in patients receiving cetuximab versus 4.1 months in patients of the radio-chemotherapy alone group. Considering these contradictory results, it becomes obvious that additional studies are required. The main goal of the present work was to identify the maximum tolerated dose of 5-FU taking into account the occurrence of DLTs by using the traditional 3+3 design. The three patients treated at dose level 1 did not experience any DLT. Therefore, one could proceed to dose level 2. Three patients were treated at this dose level and, again, no DLT occurred. Hence, both dose levels could be considered safe and feasible.

In summary, according to the results of this phase I study, 59.4 Gy of radiotherapy supplemented by chemotherapy with 20 mg/m^2 of cisplatin and 1,000 mg/m^2 of 5-FU on days 1-4 and additional weekly administration of cetuximab appeared a safe regimen. Consequently, it is used as experimental arm for a subsequent randomized phase II study (27).
Conflicts of Interest

The present investigator-initiated trial (IIT) was funded by Merck Serono. In addition to the study grant, D.R. received speaker’s honoraria and travel grants from Merck Serono.

References


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