Radio-chemotherapy with Cisplatin, 5-Fluorouracil and Cetuximab for patients with locally advanced esophageal cancers

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Abstract: **Purpose:** To evaluate the prognosis of patients with un-resectable locally advanced esophageal cancer who receiving radio-chemotherapy with 5-fluorouracil and cisplatin by addition of cetuximab. Besides, we aimed to define the maximum tolerated dose in the study. **Methods**: There were 6 victims of un-resectable locally advanced esophageal cancer were enrolled in this study who admitted to the Tri-Service General Hospital. The treatment regimen 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, dose level 1:750 mg/ m², d1-4; dose level 2: 1,000 mg/m², d1-4), followed by two courses of chemotherapy. In the meanwhile, cetuximab was given for 14 weeks (400 mg/m² loading dose followed by 250 mg/m² weekly). **Result**: At dose level 1(n=3) and 2 (n=3), no patient experienced the dose-limiting toxicity. Furthermore, minor treatment modifications were due to organization or request by physicians/patients. At dose level 2, only five grade 3 adverse events occurred. **Conclusion**: we concluded that the dose level 1 and 2 revealed safe and could be used in a subsequent randomized phase II in treat the patients with unresectable locally advanced esophageal cancer.

Keywords: locally advanced esophageal cancer, chemoradiation.

Introduction

Esophageal cancer is considered a highly aggressive malignancy. It represents the sixth most common cause of cancer-related deaths worldwide 〔1〕. There are three characters of the esophageal cancer including high incidence, poor prognosis and strong invasiveness activity affecting more than 450,000 people at a rapid increasing rate in the world 〔2,3〕. In the United States, for example, 17,000 new cases of esophageal cancer in 2016 and the type of cancer lead to over 15,000 deaths. In the UK, esophageal cancer is accounting for around 5 % of all cancer cells. The incidence of esophageal and esophageal carcinomas predominantly affecting the lower esophagus and gastro-esophagus junction has been increased substantially in recent decades. The incidence of aqueous cell carcinoma is stable or falling in the UK, but it is much prevalent in the southern and east Asia. Moreover, in China in 2015, the incidence of esophageal cancer was 679,000 cases, and the mortality was estimated at 498,000 deaths. Notably, more than 90% of esophageal cancer is pathologically diagnosed as squamous cell carcinoma in East Asia 〔4〕. Due to the advances in surgical techniques and multi-modality treatment, the prognosis of non-metastatic esophageal cancer has slowly improved over the past decades 〔5〕. Now, the usual methods for handling the esophagus carcinoma included surgery, radiation, and chemotherapy.

At first, surgical removal of the involved lesion is always first choice in the strategy regimen. Surgery has been the cornerstone of curative treatment for this disease for the past 50 years, but it is only appropriate improvements in patient population, and despite the improvement in patient selection, peri-operative care and adjuvant treatment 〔6,7〕 and those who relapse within 2 years of surgery never regain their former quality of life 〔8〕. Furthermore the earlier outcomes with surgery were poor (even by previous standards), with high rates of post-operative complication and increased properties for both local and distant failure 〔9〕. Squamous cell carcinoma of esophageal cancer is the predominant histologic type, accounting for > 90% of the cases. In clinic, the evidence showed that esophagus cancer in patients of age more than 60 or 75 years old in 44 and 30%, respectively 〔12〕. However, the overall 5-year survival probability is still poor and needs to be considerably how to

improve〔10〕. Recently (Since 2016), Kondo and his Japanese co-workers proposed that the methods of salvage endoscopic resection was endoscopic submucosal resections using a cap, strip biopsy, or dissection, However, on safe and feasible procedure on the biopsy for esophageal squamous cell carcinoma after chemoradiotherapy or radiotherapy. It would not solve the entire problems〔15〕. Now, surgery (the first choice for early-stage patients), chemistry, radiotherapy, and combination therapy such as chemotherapy together with surgery and radiotherapy are common treatment option of esophageal cancers. Although survival improvement has been already identified, treatment for esophageal cancer continues to be markedly influenced by age〔13〕. However, surgical approach in these older victims over 70 years remains controversial, due to the potentially higher post-operative complication〔14〕.

As radiation, it may own the ability to limit the growth of tumor. Afterwards, some doctors may choose the radiotherapy as the initial treatment for the patients with esophagus squamous cell carcinoma instead of surgical alone〔32〕. Using radiation therapy as a way of shrinking tumors or to treat regional disease in esophageal cancers has an extensive history. In the modern time, radiotherapy has become more refined both in its indications and in its delivery. For example, improved accuracy of delivery has allowed radiation oncologists to treat the gross tumor with smaller margins, sparing normal tissue, toxicities along the way. The range of therapeutic radiation, dosage, radiation field, and there is now considerable evidence with systemic therapy are now understood. Recently, as radiotherapy techniques become more precise and radiation toxicities lower, the wider therapeutic window in an anatomically sensitive will hopefully translate to better clinical outcomes. Now it is a principle that if surgery cannot be performed, patients are treated with definitive radiotherapy or radiochemotherapy alone, which had been the standard treatment for patients with unresctable tumors for many years, resulted in survival rates〔15〕. However, some authors found that a few types of esophageal tumors tend to be very radio-resistant meaning the use of radiotherapy even for mass reduction is limited〔27〕. Therefore, we must try another treatment regimen including using chemotherapy or radiochemotherapy for the benefit in some radio-resistant cases. For example, Herskovic et al. ever reported that the median survival was 8.9 months in the radiation-treated, as compared with 12.5 months in the patients in the patients treated with chemotherapy and radiation therapy〔28〕. Therefore, they demonstrated that concurrent therapy with chemotherapy and radiation is superior to radiation alone in patients with localized carcinoma of esophagus, as measured by control of local tumors, distant metastases and survival. Therefore, the synergic effects from various radiation and chemotherapy may be used in medical oncology in some situation. The advantage should highlight for treating various human cancers. Moreover, Byfield and his colleges found that combined therapy may result in better control of local tumor and fewer distant metastases, as well as improved survival. Because the dose of radiation was lower in the combined-therapy group, the results are compatible with the concept of radiosensitization〔29〕. In Herskovic's study, they revealed that 40% of the patients who received radiation therapy had persistent disease, and an additional 24 percent had local recurrence. Hence, the summation of radiotherapy and chemotherapy is necessary.

Carcinoma of the esophagus traditionally has been treated by surgery or radiation therapy, but 5-year overall survival rate have been only 5%-10%〔30〕. Therefore, chemotherapy has been proposed by many medical doctors recently. In clinic, chemotherapy is the effective on the target directly, and then series of chemical reaction occurs which lead to the shrinkage of the tumor. Another advantage for the trouble advanced malignant tumor and even metastases is the usage of chemotherapy which is a category of cancer treatment that uses one or more anti-cancer drugs as part of a standardized chemotherapy regimen〔20〕. Chemotherapy may be given with a curative intent (which always involves combinations of drugs), or it may aim to prolong life or to reduce symptoms (palliative chemotherapy). Le Bras and his medical team even suggested that chemoprevention may benefit for the esophageal cancer〔31〕. By the common usage, chemotherapy has come to connote the use of rather non-specific intracellular poisons, especially related to inhibiting the process of cell division known as mitosis, and generally excludes agents that more selectively block extracellular growth signals (i.e. blockers of signal transduction). To avoid these connotations, recently developed therapies (against specific molecular or genetic targets) which inhibit growth-promoting signals coming from classic endocrine hormones (for example, estrogens for breast cancer and androgens for prostate cancer) are also called hormonal therapies. Whether chemotherapy or hormonal therapy for various cancers, they are introduced into the blood stream and therefore in principle able to address cancer at any anatomic location in the body. Systemic therapy is often used in conjunction with other modalities that constitute local therapy (i.e. treatments whose efficacy is confined to the anatomic area where

they are applied) for cancer such as radiation therapy, surgery or hyperthermia therapy〔15〕.

Many of patients receive definitive radio-chemotherapy (CRT), mostly consisting of cisplatin and 5-fluorouracil (5-FU)〔45,46〕. It is questionable whether intensification of the systemic treatment could improve the outcome of these patients. Besides, cetuximab, a monoclonal epidermal growth factor receptor (EGFR) antibody, has shown considerable efficacy when combined with radiotherapy in patients with head-and-neck cancer〔45,46〕. 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 purpose 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 2015 and 2016 after giving written informed consent and received definitive radio-chemotherapy for the unresectable locally and received definitive radio-chemotherapy for unresectable locally advanced esophageal cancer.

The study protocol was approved by the ethics committee of the Tri-Service General Hospital (Taipei, Taiwan). 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.

Dose-limiting toxicities (DLTs), which were defined as any grade >3 toxicity, dose reduction of chemotherapy or radiotherapy by >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. The 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. At first, 3 patients were treated at dose level 1. If no patient experienced a DLT, the next 3 patients would have been treated at dose level 2. In case of one DLT at dose level 1, another 3 patients would have been treated at this dose level. If one of six patients at dose level 1 experienced a DLT, the next 3 patients would have been treated at dose level 2. No dose escalation was performed beyond level 2. If 2 of 3 or 2 of 6 patients, respectively, at dose level 1 experienced a DLT, the next three patients had to be treated at dose level 0. If 2 of 3 or 2 of 6 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, a delay of administration of cetuximab of more than 3 days occurred in one patient (weeks 14 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 and for 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 day 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. 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 1-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 but 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 treated at dose level 2, five grade 3 adverse events (worst case per patient) occurred, 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 probable 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 ［47,48,49,50］. 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 ［51］. 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 ［51］. The 1-year rates of locoregional control were 94%, 19% and 52%, respectively.

Locoregional recurrence is a major concern and the primary mode of failure in esophageal cancer patients treated either with surgery or definitive chemoradiotherapy. The unique lymphatic network of the esophageal and the absence of serosal covering around the organ are the two major causes of high locoregional failure after treatment ［33］. Extensive longitudinal interconnecting system of lymphatics facilitates does not early lymphatic spread of the tumors but also potential risk for lymphatic involvement longitudinally throughout the entire length of the organ rather than the segmental involvement of nodal areas. Metastases to anatomically of distant lymphatic nodes could develop even in the early phase of lymphatic invasion and up to 8 cm or more of normal tissue can exit between the gross tumor and its micro-metastases ［34］. Lymph node metastases can be observed even with superficial esophageal tumors. While the reported incidence is around 14 to 21% for T1 tumor, this chiffre rises immediately up to 60% for T2 tumor. Autopsy findings demonstrate residual or recurrent tumor in 60% of the patients after curative surgery. While local recurrence were observed in 25.6% of autopsied cases, lymph node metastases were observed in 41.% of the cases ［35］.

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. In the 1992 trial, chemotherapy included four courses of 5-FU (1,000 mg/m²/day on days 1-4) and cisplatin (75 mg/m² 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/m² cisplatin given on day 1 may be replaced by 20 mg/m² cisplatin on days 1-4 ［51,52,53,54,55］. However, the results of definitive radio-chemotherapy for esophageal cancer are still unsatisfactory and require improvement. Escalation of the radiation dose did not result in better survival rates according to the results of phase II trial. Improvement of the patients' prognosis may, therefore, be achieved with intensification of the systemic treatment.

Recently, series of chemotherapy agents should be developed and wild be used in the clinic. For example, Cisplatin (a chemotherapy medication) would be used by injection into the vein to treat several cancers which included testicular cancer (Cisplatin is particularly effective against the testicular cancer and the cure rate could improve to

85%), ovarian cancer, cervical cancer, breast cancer, bladder cancer, esophageal cancer and lung cancer 〔15,16,17,18,19〕. The mechanism of Cisplatin is in the platinum-based anti-neoplastic family of medication. More Cisplatin may work in part by binding to, and inhibiting DNA replication. However, series of side effects should be observed in detail such as Nephrotoxicity, Neurotoxicity, and Bone suppression Electrolyte's imbalance, nausea and vomiting and even hemolytic anemia etc. Therefore, we must pay attention to the severe condition while prescribed. Another famous chemotherapy agents is Fluorouracil (5-FU), it is a common medication used to treat different type of cancers. According to the past articles, 5-FU could be used for esophageal cancer, stomach cancer, pancreatic cancer, breast cancer, cervical cancer and even basal cell carcinoma 〔20,21,22,23,24,25〕. When used by injection in to 5-FU, most people develop side effects. Common side effects include inflammation of the mouth, loss of appetite, low blood cell counts, hair loss, and inflammation of the skin. When used as a cream, irritation at the site of application may occur. Use of either form in pregnancy may harm the baby. 5-FU is in the antimetabolite and pyrimidine analog families of medications. How it works is not entirely clear but believed to involve blocking the action of thymidylate synthase and thus stopping the production of DNA. However, chemotherapy is effective on the targets, the associated various side-effects should let the patients give up the success because of the troublesome problems and intolerance in clinic.

For the advanced cancers for esophageal cancers, the multi-timodal therapies such as chemo-radiation or combination chemotherapy are the current standards 〔16〕. Hence, chemo-radiotherapy when given as definite treatment is more than effective than radiotherapy or chemotherapy alone. In some advanced countries, the chemotherapy is usually offered to patients who are unsuitable for surgery. Unsuitability for surgery might be due to the extent of disease precluding the likelihood of a curative resection, or because the patient is physiologically not fit for surgery because of comorbidities or poor performance status 〔11〕. Recently, Cetuximab is highly appreciated for its stronger abilities to treat various human tumors at first line. Because it belongs to an epidermal growth factor inhibitor, cetuximab is usually used for the metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer 〔38,39,40〕. Cetuximab is a human chimeric monocular antibody given by intravenous infusion. In July 2009, the FDA approved cetuximab (Erbitux) for treatment of colon cancer and even some metastasis conditions 〔37〕.

Now some doctors favor that it is also benefit for the unresctable locally advanced esophageal cancer 〔36〕. Recently, cetuximab was approved by the FDA in March 2006 for use in combination with radiation therapy for treating squamous cell carcinoma of the head and neck or as a single agent in patients who have had prior platinum-based therapy. One of the more serious side effects of cetuximab therapy is the incidence of acne-like rash. This rash rarely leads to dose reductions or termination of therapy. It is generally reversible. Further severe infusion reactions include but are not limited to: fevers, chills, rigors, urticaria, itchiness, rash, hypotension, nausea, vomiting, headache, shortness of breath, wheezing, angioedema, dizziness, anaphylaxis, and cardiac arrest. Therefore, pretreatment with diphenhydramine (30 to 60) min before administration is standard of care. Other common side effects include photosensitivity, hypomagnesemia due to magnesium wasting and less commonly pulmonary and cardiac toxicity.

However, traditional chemotherapeutic agents are cytotoxic by means of interfering with cell division but cancer cells vary widely in their susceptibility to these agents. To our knowledge, chemotherapy can be thought of as a way to damage or stress cells, which may then lead to cell death if apoptosis is initiated. Many of the side effects of chemotherapy can be traced to damage to normal cells that divide rapidly and are thus sensitive to anti-mitotic drugs: cells in the bone marrow, digestive tract and hair follicles. These results in the most common side-effects of chemotherapy: myelosuppression, and alopecia. Because of the effect on immune cells, chemotherapy drugs often find use in a host of diseases that result from harmful over-activity of the immune system against self (so-called autoimmunity). These include some diseases: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, vasculitis and others.

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 〔56〕. 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 〔15,16,17,18,19〕. 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) 〔33〕. The 5-year survival rates were

46% and 36%, respectively〔46〕. 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 〔57,58〕. 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〔45,46,59〕. In addition, a grade ≥2 acneiform rash was reported to be a marker for response to treatment with cetuximab〔60〕. 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 radio-chemotherapy of esophageal cancer can improve the overall survival of these patients〔62,63〕. In the SCOPE1 trial, treatment included two courses of induction chemotherapy with cisplatin (60 mg/m² on day 1) and capecitabine (625 mg/m² 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 trail, patients receiving cetuximab had a worse median survival (22.1 vs. 25.4 months, p=0.035). However, the treatment programs used in the SCOPE1-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〔64〕. In contrast to the SCOPE1-trial, the preliminary results of a randomized phase II study showed a better progression-free survival (PFS) in patients receiving cetuximab in addiotion to radio-chemotherapy〔56〕. In phase II study, radio-chemotherapy included 59.4 Gy of radiotherapy plus two concurrent courses of cisplatin (20 mg/m² on days 1-4) and 5-FU (1,000 mg/m² on days 1-4) followed by two additional courses of cisplatin (20 mg/m² on days 1-4) and 5-FU (750 mg/m² 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 along 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 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.

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Conclusion

In our summary, according to the results of this phase I study, 59.4 Gy of radiotherapy supplemented by chemotherapy with 20 mg/m² of cisplatin and 1,000 mg/m² 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〔62〕.

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