ORIGINAL RESEARCH

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Docetaxel, Cisplatin, and Fluorouracil Combination Chemotherapy in Neoadjuvant Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: A Retrospective Study

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ABSTRACT Objective: Locally advanced (LA) esophagus squamous cell cancer (ESCC) is an aggressive tumor. Multimodal treatment options are being explored for ESCC. This study evaluated the efficacy and safety of docetaxel plus 5-fluorouracil and cisplatin (DCF) chemotherapy in LA ESCC. **Material and Methods:** Thirty-six patients with LA ESCC treated with DCF combination chemotherapy were retrospectively analyzed. Patients had received the DCF dosing scheme, involving docetaxel and cisplatin 75 mg/m^2 on day 1 and fluorouracil 750 mg/m^2 day on days 1-5, and this was repeated every three weeks. **Results:** The most common tumor location was the cervical esophagus (61%). T4 disease and lymph node involvement were observed in 56% and 84% of patients, respectively. After the neoadjuvant DCF application, most of the patients were treated with curative chemoradiotherapy (79%) and the remaining were operated on (17%). Clinical and objective response rates with neoadjuvant DCF applications were 75% and 59%, respectively. The median overall survival and progression-free survival was 37 (95% CI: 5-68) and 14 (95% CI: 6- 20) months, respectively. The 1- and 2-year survival rates were 70% and 50%, respectively. Treatment-related deaths were not observed. Grade 3-4 anemia (n=4, 11%), neutropenia (n=5, 14%), and thrombocytopenia (n=2, 5%) were the most common hematological toxicities in patients who were treated with classic DCF. **Conclusion:** Neoadjuvant DCF is a preferable combination of chemotherapy for young and fits LA ESCC patients.

Keywords: Esophageal squamous cell cancer, neoadjuvant chemotherapy, taxane

Esophageal cancer is the 8th most common cancer, and nearly 570, 000 people are diagnosed with esophageal cancer annually. The majority of these are squamous cell carcinoma (SCC). Esophageal cancer accounts for 1% and 6% of all cancers and gastrointestinal cancers, respectively. Esophageal cancer is more common in men than women and is a prominent cause of cancer-related death in men worldwide.[1] Surgery is the basis of esophageal cancer treatment, but the diagnostic rate of patients suitable for surgery is very low. Most of the esophageal cancers are diagnosed in the locally advanced or metastatic stage, and their prognosis is poor. Local advanced esophageal cancer (LAEC) is known to involve T3-4a or lymph node according to the 7th edition of the American Joint Committee on Cancer (AJCC) {Rice, 2010 #186}. The optimal treatment of patients with LA ESCC is controversial.[2] In such patients, local and distal recurrences are common; therefore, multimodal treatment options are applied. With randomized controlled studies, neoadjuvant chemotherapy has shown significant survival benefit.[3-7] Longer survival and good local control were reported in the patients who had the option of surgical intervention upon neoadjuvant chemoradiotherapy. However, the applicability of the triple modality (neoadjuvant

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chemoradiotherapy + surgery) is generally difficult due to weight loss and low-performance status.

The outcomes of adding neoadjuvant chemoradiotherapy or chemotherapy to surgery were extensively investigated in the past and meta-analyses have shown that neoadjuvant chemoradiotherapy is associated with significant survival benefit while chemotherapy is associated with survival benefit only in patients suffering from adenocarcinoma of esophagus.[8]

A randomized trial was conducted comparing cisplatin and 5-fluorouracil (CF) combination chemotherapy preoperative to postoperative in stage 2-3 esophageal SCC. This study showed neoadjuvant CF to be more effective than the use of adjuvant.[7] Docetaxel has been used in combination with chemotherapy in various cancers, such as head, neck, and gastric cancers. Recently, preoperative chemotherapy using docetaxel, 5-fluorouracil, and cisplatin (DCF) was investigated in research trials.[9-11] However, data on DCF induction chemotherapy is very limited in LA ESCC. The aim of this study was to evaluate the efficacy and safety of combination DCF chemotherapy in locally advanced esophageal SCC.

MATERIAL AND METHODS

PATIENT AND METHODS

Data of 36 patients with LA ESCC who were treated with DCF neoadjuvant chemotherapy from January 2010 to March 2016 were retrospectively analyzed. This study was approved by the institutional ethics committee(27.5.2015/GO-15368).

The demographic features of the patients and tumor pathological characteristics, duration of DCF treatment, its adverse effects, and responses were recorded. DCF was administered, which involved 3-week cycles of 75 mg/m^2 docetaxel and cisplatin on the first day, followed by continuous infusion of 750 mg/m^2 fluorouracil for five days. Granulocyte colony-stimulating factors were routinely used after each DCF cycle. Neoadjuvant DCF was applied in three cycles. The DCF dose was modified in eight elderly patients with poor performance. The file records revealed that each newly diagnosed patient was evaluated in the tumor council. Definitive CRT was offered to the patients who refused operation or in case of high-risk surgery. The physician adjusted the chemotherapy dose according to the patient's toxicity. After three cycles of chemotherapy, response evaluations were done through the Response Evaluation Criteria in Solid Tumors Version (RECIST). Side effects were recorded according to the Common Terminology Criteria for Adverse Events (version 4.0).

STATISTICAL ANALYSIS

All statistical analyses were performed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc. Chicago, IL, USA). The sample dataset was characterized using standard descriptive statistics. Overall survival and progression-free survival were calculated using the Kaplan-Meier method. Comparison of survival curves was performed using the log-rank test. Two-sided p-values < 0.05 were considered as statistically significant.

RESULTS

The median age of the patients was 50 (range, 17–71) years. Twenty patients (55.5%) were women. The demographic features of the patients are presented in Table 1. The most common tumor location was the cervical esophagus (61%). Fifty-six percent of patients had T4 disease, among which, 20% were T4b. Lymph node involvement was observed in 28 patients (84%). Most patients were in the advanced stage (33% and 47% of patients were in stage 3a and 3c, respectively).

All patients had completed the DCF neoadjuvant chemotherapy. Following DCF neoadjuvant chemotherapy, the complete and partial response rates (RRs) were 6% and 53%, respectively, and the objective response rate (ORR) was 59% (Table 2). Also, no difference in ORR was observed between cervical and thoracic esophageal cancer. In cervical cancer patients, partial response (PR) and stable disease (SD) were observed in 9 and 5 patients, respectively. Response in thoracic-esophageal cancer patients, SD, and PR were observed in 9 and 2 patients, respectively.

After DCF neoadjuvant chemotherapy, most patients (79%) were treated with curative chemora-

TABLE 1: Demographics and clinical features of the patients detected with esophageal cancer.

Parameters	Whole group N (%)
Age	50 (17–71).
Gender (F/M)	20/16
Location of tumor (%)	
Cervical	22 (61)
Thoracic	14 (39)
Clinical T stage	
T2	6 (16)
T3	10 (28)
T4	20 (56)
T4a	13 (39)
T4b	7 (20)
Clinical N stage	
N0	6 (16)
N+	30 (84)
TNM	
2b	7 (20)
3a	12 (33)
3c	17 (47)

diotherapy, and only six (17%) patients were treated with surgery. Two patients with cervical involvement and four patients with thoracic involvement were operated on. The median follow-up time was 16.5 (range, 1-50) months. The median overall survival (OS), and progression-free survival (PFS) were 37 (95% CI: 5-68) months and 14 (95% CI: 6-20) months, respectively. The 1- and 2-year OS rates were 70% and 50%, respectively, and the 1- and 2-year PFS rates were 72% and 41%, respectively (Figure 1 and Figure 2). The median OS durations were 37 and 16 months for stage 3a and 3c, respectively, and the median OS was not reached in stage 2b.

TABLE 2: Outcomes of the study groups.

Outcomes	c.DCF, n (%)
CR	2 (6)
PR	19 (53)
SD	6 (17)
PD	9 (25)
CBR (CR+ PR+ SD)	27 (75)
ORR (CR+ PR)	21(59)

CR: complete response, PR: partial response, ORR: objective response rate defined as CR + PR, CBR: Clinical benefit rate defined as CR+ PR+ SD, SD: stable disease, PD: progressive disease.

The toxicities of the DCF regimen observed during the treatment periods are mentioned in Table 3. In total, 41% of patients developed neutropenia, and 36% of patients developed thrombocytopenia. Grade 3-4 neutropenia, anemia, and thrombocytopenia were observed in, 14% (n=5), 11% (n=4), and 5% (n=2) of patients, respectively. Febrile neutropenia was observed in four patients (11%). Nausea/vomiting and diarrhea were the most common non-hematological toxicities, and these toxicities in grades 3-4 were observed in 14% (n=5) and 5% (n=2) of patients, respectively.

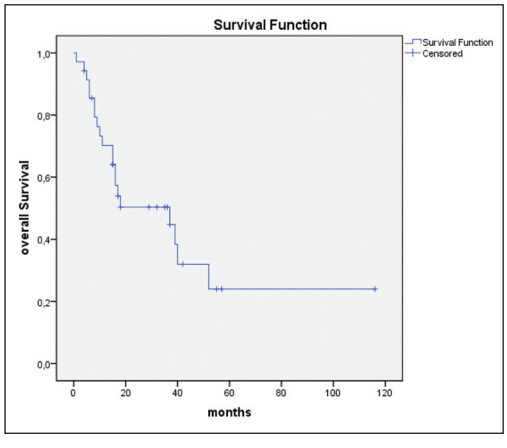


FIGURE 1: Kaplan–Meier curve to assess overall survival.

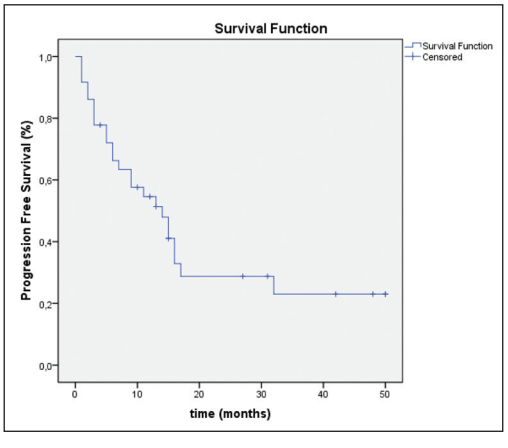


FIGURE 2: Kaplan–Meier curve to assess progression-free survival.

TABLE 3: Adverse events associated with induction chemotherapy.

Parameters	Grade 1-2, n (%)	Grade 3-4, n (%)	Total
Hematologic toxicity			
Neutropenia	11 (30)	5 (14)	15 (41)
Febrile neutropenia	-	-	4 (11)
Anemia	23 (63)	4 (11)	27 (75)
Thrombocytopenia	11 (30)	2 (5)	13 (36)
Non-hematological toxicity			
Nausea/vomiting	15 (41)	5 (14)	20 (59)
Diarrhea	5 (14)	2 (5)	7 (19)
Mucositis	3 (8)	2 (5)	5 (14)
Renal toxicity	2 (5)	0	2 (5)
Hepatic toxicity	1 (3)	0	1 (3)

DISCUSSION

This study demonstrates that high response rates can be achieved with induction DCF chemotherapy in locally advanced ESCC patients. The clinical benefit rate and ORR of this study were 75% and 59%, respectively. The median PFS was 14 (95% CI: 6-20) months, and the median OS was 37 (95% CI: 5-68) months. One- and 2-year OS rates were 70% and 50%, respectively.

Multimodal treatments have been used to increase the success rate in locally advanced ESCC. Some studies have investigated the efficacy of neoadjuvant chemotherapy.[3-6] Neoadjuvant chemotherapy is found to be more effective in patients with esophageal adenocarcinoma than esophageal SCC. Some studies proved the survival benefit with neoadjuvant chemotherapy using CF in patients with ESCC.[6,7] Based on the results of these studies, CF has been used as the standard neoadjuvant regimen for advanced EC. However, the ORR and survival period were 25%–35% and 9.2 months, respectively. Recently, a triplet regimen comprising the addition of another drug to CF was introduced. Adriamycin, in addition to CF (FAP) and docetaxel with CF (DCF) have also been reported as candidate neoadjuvant chemotherapies for EC and have demonstrated RRs of 55.6% and 62%, respectively, in recent studies.[12,13].

Several trials have demonstrated that DCF induction chemotherapy greatly increases RRs in patients with ESCC (Table 4).[13-17] In a phase II trial, patients with LA ESCC who had undergone DCF treatment were evaluated.[14] In the study, patients with T4 and/or supraclavicular lymph node metastasis were taken, and the ability to proceed with surgery with DCF was evaluated. ORR was 31%, and 39% of the patients were operated on. Median survival could not be achieved, and the first-year survival was 67%. In the present study, this difference can be explained because there are different patient groups.

In another phase II study, in which 37 local advanced ESCCs were included, CRT was planned after neoadjuvant DCF[13]. The clinical response rate was 49% and 12 (32%) patients were operated on. Also, the median OS was 10.8 months; however, in the present study, ORR and median OS were higher (59% and 37 months, respectively). The difference in the results might be explained by the variations in the median age of the patients (who were younger in this study) and in the rates of T2 disease (16% in the current study versus 3% in the other study). DCF chemotherapy combination is a toxic regimen and can be tolerated by mostly young patients.

In another phase II trial, neoadjuvant DCF treatment was evaluated in stage 2 or 3 thoracic ESCC.[17]

TABLE 4: Reports of DCF treatment in esophageal SCC.

Authors	Analysis	Year	n	DCF	ORR	OS months
V Chiarion-Sileni[13]	Phase II	2007	31	60/75/750	49%	10.8
Tomoya yokota[14]	Retrospective	2011	30	60–70/60–70/750–800	10/16(62%)	35.9
Makoto Yamasaki[15]	Phase I-II	2011	40	60–75/70/700	72.5%	14
Yoshihiro Tanaka[16]	Phase I	2010	18	30–40/40/400	NA	NA
Hiroki H[17]	Phase II	2013	42	70–75/70–75/750	64.3%	NA

ORR: objective response rate, OS: overall survival, NA: not applicable.

After three cycles of DCF treatments, the patients underwent surgery. The overall response rate and pathologically complete RR were achieved in 64% and 17% of patients, respectively. The estimated 2-year PFS and OS rates were 74.5% and 88%, respectively. In the current study, second year PFS and OS were 41% and 50%, respectively. This difference may be attributed to the selection of patients with better ECOG Performance Score compared to retrospective real-life data. In addition, while all patients in the phase II study had esophageal cancer in the thoracic region, most of them were located in the cervical esophagus in the current study. Patients with cervical esophagus cancer have a worse prognosis.

Triplet regimens such as DCF increase the response rates but are more toxic. In our study, the most common hematological toxicity was grade 3-4 neutropenia, which was observed in 14% of patients in the c.DCF scheme. With the application of granulocyte colony-stimulating factors, febrile neutropenia was observed in only 11% of patients. Besides, grade 3-4 anemia and thrombocytopenia were observed in 11% and 5% of patients, respectively, while grade 3-4 nausea-vomiting, diarrhea, and mucositis were seen in 14% and 5%, respectively. Generally, the adverse effects of DCF are well tolerable and manageable, especially in young patients.

There were some limitations in our study. This was a retrospective study, and the number of patients was not sufficient to evaluate the effectiveness of DCF in terms of some variables, such as tumor localization, and tumor and lymph node status. The side effects are evaluated as retrospective file scanning; therefore, the accuracy rate may not be as high as that reported in clinical studies. In addition, the study groups were almost heterogeneous. Nevertheless, given the strong response rates and survival benefit, the combination of DCF chemotherapy can be considered as a treatment option for young patients.

In conclusion, the results reveal that DCF induction chemotherapy is preferable for young and fit LA ESCC patients; however, studies must be conducted on a larger patient population to confirm this result.

Compliance with ethical standards: Ethical statement: “This article does not contain any studies with human or animal subjects performed by any author(s).”

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Şuayib Yalçın;* ***Design:Öztürk Ateş; Control/Supervision:*** *Saadettin Kılıçkap;* ***Data Collection and/or Processing:*** *Emre Yekedü;* ***Analysis and/or Interpretation:*** *Saadettin Kılıçkap;* ***Literature Review:*** *Öztürk Ateş;* ***Writing the Article:*** *Öztürk Ateş;* ***Critical Review:*** *Saadettin Kılıçkap;* ***References and Fundings:*** *Öztürk Ateş.*

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