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Retrospective Study

Efficacy of concurrent chemoradiotherapy with thalidomide and S-1 for esophageal carcinoma and its influence on serum tumor markers

INTRODUCTION

Esophageal carcinoma (EC) is a common fatal gastrointestinal (GI) tumor with a five-year survival rate of only 15%–25%. It is characterized by high malignancy, invasiveness, and easy metastasis[1]. According to global statistics, EC is broadly pathologically classified into esophageal squamous cell carcinoma and esophageal adenocarcinoma; the former is primarily distributed in Southeast Asia and Africa and the latter in Europe and North America[2,3]. Onco-pathologically, EC is shown to be associated with the abnormal proliferation of esophageal epithelial cells that induces invasive cancer or invasive adenocarcinoma; meanwhile, the etiology is related to factors such as esophageal mucosa contact with carcinogens and mechanical damage[4,5]. Moreover, the disease is mainly presented clinically as dysphagia and unexpected weight loss but usually with no specific early symptoms[6]. At the present stage, EC is mainly treated with surgical resection, radiotherapy, and chemotherapy. Despite the confirmed effectiveness of these conventional treatments, they are accompanied by serious adverse events, resulting in unsatisfactory clinical outcomes[7]. Therefore, there is an urgent need to explore new strategies for treating EC and optimizing the treatment options for patients with EC; this can be of great value for improving treatment efficacy as well as patient prognosis and symptoms.

Thalidomide (THAL), which was originally used as a sedative for the relief of vomiting and nausea during pregnancy, has been used to treat solid tumors because of

its anti-angiogenesis effects[8]. Its anti-tumor mechanism is reported to be linked to the regulation of the secretion of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)[9]. Another molecular study shows that THAL exerts immunomodulatory actions by altering the expression of tumor necrosis factor receptor superfamilies in T cell subsets[10]. The fluorouracil drug S-1 consists of tegafur, gimeracil, and oteracil potassium. It can be used to treat gastric, pancreatic, gallbladder, colorectal, and esophageal cancers[11,12] and has been shown to not only exert better anticancer performance than 5-fluorouracil (5-FU) but also reduce cancer cells' resistance to chemotherapy[13]. In the analysis by Wang *et al*[14], definitive concurrent chemoradiotherapy (CCRT) with S-1 and cisplatin significantly improved the survival outcomes of older adults (≥ 60 years old) with EC.

The present study attempts to analyze the effectiveness of CCRT with THAL + S-1 for EC and its influence on serum tumor markers (STMs) in order to provide a new feasible scheme for improving the survival outcome of patients with EC.

MATERIALS AND METHODS

Patient information

The study population comprised 62 patients with EC treated at the Zibo 148 Hospital between November 2019 and November 2022. The patients were grouped according to the received treatment. A total of 30 patients undergoing CCRT with cis-platinum (DDP) and 5-FU were assigned to the control group (Con), and 32 patients receiving CCRT with THAL and S-1 were assigned to the research group (Res). The Con consisted of 17 males and 13 females with a mean age of 61.03 ± 6.91 years, and the Res consisted of 19 males and 13 females with a mean age of 61.44 ± 10.61 years. The present study is retrospective.

Criteria for patient enrollment and exclusion

Inclusion criteria: (1) patients gastroscopically and pathologically diagnosed with EC and meeting the American Joint Committee on Cancer clinical staging criteria for EC;

(2) patients with a life expectancy of three or more months; (3) patients with a Karnovsky Performance Scale score of ≥70 points; (4) patients capable of eating semi-liquid food; and (5) patients with normal hepatorenal function and blood routines.

Exclusion criteria: (1) patients with an intolerance to the treatment scheme of the present study; (2) patients with other malignancies; (3) patients with hepatic fibrosis, (4) patients with renal fibrosis and other systemic fibrosis; (5) patients undergoing chemotherapy or other adjuvant treatment programs; and (6) patients with distant metastasis of the tumor.

Methods

All patients received three-dimensional intensity modulated radiation therapy. Gross tumor volume and organs at risk were delineated according to the pathology and imaging findings, and treatment schemes were specified based on patients' conditions. The prescribed dose was 56–70 Gy, with a single dose of 2 Gy administered five times a week for four weeks. Of these, 95% of the planned target area was irradiated with a prescription dose of at least 100% for the whole lung, no more than 25%–30% for V20, and no more than 18% for V30; the upper limits were set at 30 Gy and 45 Gy for the heart and the spinal cord, respectively.

The Con was treated with CCRT using DDP + FU. Cisplatin 20 mg/(m^2·d) and 5-FU 500 mg/(m^2·d) were given intravenously for 5 consecutive days; patients received two cycles of CCRT, which were performed at week 1 and week 4 of radiotherapy, respectively.

The Res received CCRT using THAL + S-1. Patients were given S-1 capsules, 40 mg/time, twice a day from day 1 to day 14; this was repeated every 21 days simultaneously with radiotherapy. The THAL was administered at a dose of 100 mg/d before bedtime in the first week and gradually increased to 200 mg/d in the second week until the end of radiotherapy. Patients in both groups were given symptomatic treatments, such as antiemesis, stomach protection, and nutritional support during

chemotherapy, with their blood routines and hepatorenal function monitored weekly and biweekly, respectively.

Outcome measures

Short-term efficacy: The clinical efficacy, which was evaluated with reference to the Response Evaluation Criteria in Solid Tumors, was determined as complete response (CR; the tumor disappeared completely, with smooth margins shown by the barium meal test, smooth passage of the barium agent, slightly rigid tube wall, no narrowing or slight narrowing of the lumen, and basically recovered or thickened mucosa), partial response (PR; most of the lesions disappeared without obvious distortion, angulation, or extraluminal ulcer; the barium passed smoothly, but the edges were not smooth, with small filling defects or niches, or the lumen was obviously narrowed, although the edges were smooth), stable disease (SD; the lesion had residual or no obvious improvement at the end of radiotherapy, with obvious filling defects or niches), or progressive disease (worsened niche or stenosis). The overall response rate (ORR) is the sum of patients with CR and patients with PR as a percentage of the total number of cases. The disease control rate (DCR) is the sum of the percentages of CR, PR, and SD. The short-term efficacy was evaluated after radiotherapy in both groups.

Incidence of drug toxicities: The adverse reactions of anticancer drugs were classified into grades I–II or III–IV according to the WHO classification of adverse drug reactions, and the number of cases of myelosuppression (MS), GI reactions, and radiation esophagitis (RE) as well as the percentages of the corresponding side effect grades were recorded.

Serum tumor markers and angiogenesis-related indicators: Before and after treatment, 5 mL of venous blood was collected on an empty stomach during the morning hours and sent to the laboratory for examination after centrifugation. The levels of carbohydrate antigen 125 (CA125), macrophage inflammatory protein-3α (MIP-3α),

VEGF, VEGF receptor-1 (VEGFR-1), bFGF, and angiogenin-2 (Ang-2) were determined by the enzyme-linked immunosorbent assay (ELISA).

Quality of life (QoL): Patients' QoL was assessed and compared at one month after treatment, using the QoL Questionnaire core 30. The scale includes five functional dimensions: body, role, emotion, cognition, and social function. A higher score suggests a better QoL.

Statistical analysis

In the present study, the SPSS 22.0 software was used for data analysis, and GraphPad Prism 7.0 was used for image rendering and export. The significance threshold was $P < 0.05$. mean ± SEM was used for statistical description of continuous variables (*e.g.*, age, tumor diameter, and CA125 expression), and the *t*-test and paired *t*-test were used for inter-group and intra-group comparisons (before and after treatment), respectively. Categorical variables (*e.g.*, sex, clinical staging, and history of alcoholism) were described by frequencies (percentages), and the comparison between groups was made using the χ^2 test.

RESULTS

Baseline data

As indicated by Table 1, the two patient cohorts have no evident differences in age, sex, clinical staging, tumor diameter, alcoholism history, smoking history, and family history ($P > 0.05$).

Short-term efficacy in the two patient groups

The short-term curative effects between the Res and the Con at one month after treatment were analyzed and compared (Table 2). The ORRs of the Res and the Con were determined as 62.50% and 60.00%, respectively, while the DCRs were determined

as 87.50% and 83.33%, respectively, showing no significant inter-group differences in both indicators ($P > 0.05$).

Incidence of drug toxicities in the two patient groups

The main drug toxicities were MS, GI reactions, and RE, with the incidence of grade I–II MS and grade I–II GI reactions markedly lower in the Res compared with the Con ($P < 0.05$; Table 3).

Serum tumor markers in the two patient groups

Two STMSs, CA125 and MIP-3α, were measured; no statistical differences were found in the corresponding pre-treatment levels between the Res and the Con ($P > 0.05$); a marked reduction in both indexes was determined in the two patient cohorts, especially in the Res ($P < 0.05$; Figure 1).

Angiogenesis-related indexes in the two patient groups

The angiogenesis-related indexes VEGF, VEGFR-1, bFGF, and Ang-2, were determined in both groups for comparative analysis (Figure 2). The VEGF, VEGFR-1, bFGF, and Ang-2 Levels were similar in the two cohorts before treatment ($P > 0.05$), but their levels reduced significantly after treatment ($P < 0.05$), with even lower levels in the Res ($P < 0.05$).

Quality of life in the two patient groups

The QoL of the two groups was compared and evaluated from five aspects: physical, role, emotional, social, and cognitive function (Figure 3). The data showed that with the exception of cognitive function, the aspect scores in the two groups increased significantly after treatment ($P < 0.05$), with more marked increases in the Res when compared with the Con ($P < 0.05$).

DISCUSSION

The present study focuses on the efficacy of CCRT with THAL + S-1 for EC and its influence on patient STMs. Given the current scanty of research in this field, the present analysis is helpful in gaining a new understanding of the effectiveness of this CCRT protocol for patients with EC.

Many researchers have provided clinical references for EC treatment by analyzing relevant treatment strategies. For example, Song *et al*[15] showed that CCRT with S-1 effectively enhanced the curative effect and survival of elderly patients with non-metastatic esophageal squamous cell carcinoma compared with radiotherapy alone without increasing acute adverse reactions. As reported by McDowell *et al*[16], intensity-modulated radiotherapy combined with chemotherapy is conducive to improving the prognosis of patients with cervical EC. Ma *et al*[17] also pointed out that three-dimensional conformal radiotherapy was helpful in controlling mediastinal lymph node metastasis and recurrence after EC surgery, in addition to significantly improving the local tumor control rate and long-term survival rate. In the present study, the effectiveness of DDP + 5-FU *vs* THAL + S-1 were analyzed. The standard CCRT scheme for EC (DDP + 5-FU) still causes local failures in 46% of patients and fatal threats in 20%[18]. Hence, introducing new CCRT schemes is critical. Thalidomide can exert anti-inflammatory and immunosuppressive actions by inhibiting inflammatory factors and regulating key immunoregulatory molecules, thus exerting anti-tumor activity[19]. Among the S-1 components, tegafur is a prodrug of 5-Fu, and gimeracil can prolong the effective drug properties of 5-Fu in the blood by reducing dihydropyrimidine dehydrogenase[20].

In the present study, the Res was administered with THAL + S-1 and the Con was administered with DDP + 5-FU. The ORR and DCR of the Res were determined as 62.50% and 87.50%, respectively (slightly higher than but not significantly different from those in the Con); these results suggest equivalent curative efficacy of THAL + S-1 to that of DDP + 5-FU. Furthermore, according to the investigation of drug toxicities, the incidences of grade I–II MS and grade I–II GI reactions were identified as notably lower in the Res than in the Con, while the incidence of RE was similar, indicating the

safety profile of THAL + S-1. This may be related to the inhibition of FU-related GI toxicity by oteracil potassium, one of the S-1 components[20].

Previous literature has shown a correlation of CA125 with lymph node metastasis and blood-borne metastasis of EC, as well as an association between MIP-3α (also known as CCL20) and the occurrence, development, and metastasis of EC[21,22]. While VEGF and VEGFR-1 are both significantly related to the poor prognosis of patients with EC[23], previous studies have also shown that abnormal overexpression of bFGF in advanced esophageal squamous cell carcinoma is closely associated with the development of invasive carcinoma. As a key regulator of tumor angiogenesis, Ang-2 also mediates the malignant procession of esophageal squamous cell carcinoma[24,25].

By further quantifying STMs (CA125 and MIP-3α) and angiogenesis-related indicators (VEGF, VEGFR-1, bFGF, and Ang-2) using ELISA, it was found that the post-treatment CA125, MIP-3α, VEGF, VEGFR-1, bFGF, and Ang-2 Levels in the Res were evidently lower than those before treatment and the Con levels. This suggests that CCRT with THAL + S-1 has a significant inhibitory effect on STMs and angiogenesis-related indicators in patients with EC.

In the research of Wang *et al*[26], THAL validly suppressed the increase of the serum VEGF level in patients with EC during treatment; this is similar to our research results. Tsuji *et al*[27] also reported the inhibitory action of S-1 against VEGF levels in patients with metastatic breast cancer, indicating certain anti-angiogenesis activity of S-1. Finally, the QoL of the two groups after treatment was evaluated and compared regarding five aspects: physical, role, emotional, social, and cognitive function. The Res was found to have higher scores in all the other four dimensions after treatment except the cognitive function, suggesting that THAL + S-1 is more effective than DDP + 5-FU in enhancing QoL in patients with EC.

CONCLUSION

Taken together, CCRT with THAL + S-1 is effective in the treatment of EC, with certain safety. This CCRT protocol has a significant inhibitory effect on STMs (CA125 and MIP-

3α) and angiogenesis-related indicators (VEGF, VEGFR-1, bFGF, and Ang-2) and is conducive to improving patients' QoL, providing a new choice for clinical treatment of patients with EC. In addition, since the sample size included in the present study is limited, increasing the sample size in the future will be conducive to enhancing the credibility of the experimental results.

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Figure Legends

Figure 1 Serum tumor markers in two groups of esophageal cancer patients. A: The research group had markedly lower CA125 levels than the control group after treatment; B: The research group had markedly lower MIP-3α levels than the control group after treatment. $^{a}P < 0.05$ *vs* control; $^{b}P < 0.01$, *vs* before treatment. CA125: Carbohydrate antigen 125; MIP-3α: Macrophage inflammatory protein-3α.

Figure 2 Angiogenesis-related indexes in two groups of esophageal cancer patients. A: The research group had markedly lower VEGF levels than the control group after treatment; B: The research group had markedly lower VEGFR-1 Levels than the control group after treatment; C: The research group had markedly lower bFGF levels than the control group after treatment; D: The research group had markedly lower Ang-2 levels than the control group after treatment. $^{a}P < 0.05$ *vs* control; $^{b}P < 0.01$, *vs* before treatment. VEGF: Vascular endothelial growth factor; VEGFR-1: Vascular endothelial growth factor receptor-1; bFGF: Basic fibroblast growth factor; Ang-2: Angiogenin-2.

Figure 3 Quality of life of esophageal cancer patients. A: The research group had markedly higher physical function scores than the control group after treatment; B: The research group had markedly higher role function scores than the control group after treatment; C: The research group had statistically higher emotional function scores than the control group after treatment; D: The research group had markedly higher social function scores than the control group after treatment; E: The research group had obviously higher cognitive function scores than the control group after treatment. $^{b}P < 0.01$, *vs* before treatment.

Table 1 Baseline information

Indicators	Control group (n = 30)	Research group (n = 32)	χ^2/t value	P value
Age (years old)	61.03 ± 6.91	61.44 ± 10.61	0.179	0.859
Gender (male/female)	17/13	19/13	0.047	0.829
Clinical staging (II /III)	18/12	16/16	0.625	0.429
Tumor diameter (cm)	5.68±1.29	5.80±1.50	0.337	0.738
History of alcoholism (with/without)	11/19	8/24	0.992	0.319
History of smoking (with/without)	8/22	7/25	0.194	0.660
Family medical history (yes/no)	5/25	9/23	1.163	0.281

Table 2 Short-term efficacy of two groups of esophageal carcinoma patients, n (%)

Indicators	Control group (n = 30)	Research group (n = 32)	χ^2 value	P value
Complete response	6 (20.00)	7 (21.88)	-	-
Partial response	12 (40.00)	13 (40.63)	-	-
Stable disease	7 (23.33)	8 (25.00)	-	-
Progressive	5 (16.67)	4 (12.50)	-	-

disease				
Overall response rate	18 (60.00)	20 (62.50)	0.041	0.840
Disease control rate	25 (83.33)	28 (87.50)	0.217	0.642

Table 3 Incidence of drug toxicities in two groups of esophageal carcinoma patients, *n* (%)

Indicators	**Control group (*n* = 30)**	**Research group (*n* = 32)**	**χ^2 value**	**P value**
Myelosuppression				
I-II	13 (43.33)	6 (18.75)	4.403	0.036
III-IV	6 (20.00)	2 (6.25)	2.605	0.107
Gastrointestinal reactions				
I-II	15 (50.00)	8 (25.00)	4.147	0.042
III-IV	7 (23.33)	3 (9.38)	2.230	0.135
Radiation esophagitis				
I-II	14 (46.67)	13 (40.63)	0.230	0.632
III-IV	7 (23.33)	6 (18.75)	0.196	0.658

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