Original Article

Effectiveness and safety of camrelizumab-containing neoadjuvant therapy in patients with esophageal squamous cell carcinoma: a prospective multicenter observational cohort study

Yi Zhang[1], Guoyi Shen[1], Rongyu Xu[2], Guozhong Huang[3], Zhijun Huang[4], Hongbing Duan[5], Shengsheng Yang[6], Qingfeng Zheng[7], Libao Yang[8], Rongxing Liu[9], Liangyun Ma[10], Shaogeng Chen[2], Yunfeng Yi[11], Zheming Zhang[12], Kezhi Li[13], Thomas J. Birdas[14], Kazuo Koyanagi[15], Charles B. Simone II[16]

[1]Department of Cardiothoracic Surgery, Zhangzhou Hospital Affiliated to Fujian Medical University, Zhangzhou, China; [2]Department of Thoracic Surgery, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, China; [3]Department of Thoracic Surgery, Affiliated Hospital of Putian University, Putian, China; [4]Department of Gastrointestinal and Esophageal Surgery, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, China; [5]Department of Thoracic Surgery, Zhongshan Hospital Affiliated to Xiamen University, Xiamen, China; [6]Depatment of Cardiothoracic Surgery, The 900th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army, Fuzhou, China; [7]Department of Thoracic Surgery, Fujian Cancer Hospital, Fuzhou, China; [8]Department of Thoracic Surgery, Sanming Second Hospital, Sanming, China; [9]Depatment of Cardiothoracic Surgery, Longyan Second Hospital, Longyan, China; [10]Department of Thoracic Surgery, The 910th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army, Quanzhou, China; [11]Depatment of Cardiothoracic Surgery, Southeast Hospital affiliated to Xiamen University, Xiamen, China; [12]Department of Thoracic Surgery, The 900th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army Putian Medical District, Putian, China; [13]Department of Thoracic Surgery, Nanping First Hospital, Nanping, China; [14]Division of Cardiothoracic Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA; [15]Department of Gastroenterological Surgery, Tokai University School of Medicine, Kanagawa, Japan; [16]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center and New York Proton Center, New York, NY, USA

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Correspondence to: Rongyu Xu, MD. Department of Thoracic Surgery, Quanzhou First Hospital Affiliated to Fujian Medical University, 248–252 East Street, Licheng District, Quanzhou 362000, China. Email: xry641127@sina.com.

Background: Camrelizumab has been demonstrated to be a feasible treatment option for locally advanced esophageal squamous cell carcinoma (ESCC) when combined with neoadjuvant chemotherapy. This trial was conducted to investigate the effectiveness and safety of camrelizumab-containing neoadjuvant therapy in patients with ESCC in daily practice.

Methods: This prospective multicenter observational cohort study was conducted at 13 tertiary hospitals in Southeast China. Patients with histologically or cytologically confirmed ESCC [clinical tumor-node-metastasis (cTNM) stage I–IVA] who had received at least one dose of camrelizumab-containing neoadjuvant therapy were eligible for inclusion.

Results: Between June 1, 2020 and July 13, 2022, 255 patients were enrolled and included. The median age was 64 (range, 27 to 82) years. Most participants were male (82.0%) and had clinical stage III–IVA diseases (82.4%). A total of 169 (66.3%) participants underwent surgical resection; 146 (86.4%) achieved R0 resection, and 36 (21.3%) achieved pathological complete response (pCR). Grades 3–5 adverse events (AEs) were experienced by 14.5% of participants. Reactive cutaneous capillary endothelial proliferation occurred in 100 (39.2%) of participants and all were grade 1 or 2.

Conclusions: Camrelizumab-containing neoadjuvant therapy has acceptable effectiveness and safety profiles in real-life ESCC patients.

Keywords: Esophageal squamous cell carcinoma (ESCC); neoadjuvant therapy; camrelizumab; real world

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Introduction

Esophageal cancer (EC) is one of the most common cancers, with approximately 600,000 new cases and 544,000 deaths estimated worldwide in 2020 (1). Esophageal squamous cell carcinoma (ESCC) is the most common subtype in many countries, accounting for almost 90% of all EC cases in China. For patients with locally advanced EC, neoadjuvant chemotherapy or chemoradiotherapy followed by surgery have been adopted as the standard of care. However, almost 50% of the patients develop recurrent diseases within 5 years (2,3). More effective systemic treatment strategies continue to be needed to improve patient prognosis.

Cancer immunotherapy targeting programmed cell death 1 (PD-1) or its ligand (PD-L1) has been suggested as a solution. In the neoadjuvant setting, immunotherapy offers an early opportunity to eliminate micro-metastatic diseases and enhance systemic antitumor immunity (4). Additionally, the combination of immunotherapy and chemotherapy may work synergistically (5). Emerging evidence has shown exciting pathological complete response (pCR), a longstanding surrogate endpoint for EC, and manageable toxicity of neoadjuvant immunotherapy plus chemotherapy or chemoradiotherapy in resectable EC (6-9).

Camrelizumab, a fully humanized anti-PD-1 antibody, has shown promising survival benefits in the treatment of advanced ESCC patients either alone in the second-line setting or in combination with chemotherapy in the first-line setting, according to the phase III ESCORT and ESCORT-1st trials (10,11). In recent phase II studies of locally advanced ESCC, neoadjuvant camrelizumab plus nab-/paclitaxel and carboplatin or cisplatin showed encouraging antitumor activity and acceptable safety profiles (12-14). Based on these results, neoadjuvant camrelizumab plus chemotherapy has been recommended as a treatment option for locally advanced thoracic ESCC in China. The effectiveness and safety of camrelizumab-containing neoadjuvant therapy in resectable ESCC have also been investigated (15-18). However, all of these studies were retrospective, and the number of patients analyzed has generally been small. In this regard, we designed this prospective observational study to better investigate the effectiveness and safety of camrelizumab-containing neoadjuvant therapy in a comparatively large number of patients with ESCC encountered in real world daily practice. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1408/rc).

Highlight box

Key findings

- In this prospective observational study, camrelizumab-containing neoadjuvant therapy showed acceptable effectiveness and safety profiles in patients with esophageal squamous cell carcinoma (ESCC) in daily practice.

What is known and what is new?

- Neoadjuvant camrelizumab plus chemotherapy has been recommended as a treatment option for locally advanced thoracic ESCC.
- We reported the real-world effectiveness and safety of camrelizumab-containing neoadjuvant therapy in a comparatively large number of ESCC patients.

What is the implication, and what should change now?

- This study supports camrelizumab-containing neoadjuvant therapy as a suitable treatment for ESCC patients. However, the optimal treatment strategies (e.g., combination, duration) need to be explored to better guide clinical practice.

Methods

Study design and patients

This prospective multicenter observational cohort study was conducted at 13 tertiary hospitals in Southeast China. Patients with histologically or cytologically confirmed ESCC [clinical tumor-node-metastasis (cTNM) stage I–IVA] who were scheduled for camrelizumab-containing neoadjuvant therapy at the discretion of the treating physicians between May 2020 and March 2022 were screened for eligibility. Patients had to have received at least one dose of camrelizumab-containing neoadjuvant therapy

to be eligible for inclusion.

This study was reviewed and approved by the China Ethics Committee of Registering Clinical Trials (No. ChiECRCT20200264) and the Institutional Review Board of Zhangzhou Hospital Affiliated to Fujian Medical University (No. 2022LWB127) and was conducted in accordance with the Declaration of Helsinki (revised in 2013). All participating hospitals were informed and agreed with the study. All patients provided written informed consent. The study was registered with the Chinese Clinical Trials Registry (ChiCTR2000039170).

Treatments

Tumors were staged with computed tomography (CT), magnetic resonance imaging (MRI), and/or esophageal endoscopy according to the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system (19). Positron emission tomography (PET)-CT was optional. All treatments were initiated by the treating physicians. Camrelizumab was administered intravenously at a dose of 200 mg in a 3-week cycle either alone or in combination with chemotherapy. Patients were then assessed for eligibility for surgery. Those eligible proceeded to surgery according to the Institutional Standard Procedures. Postoperative adjuvant therapy was prescribed according to the clinical conditions of patients by the treating physicians.

Clinical outcomes

Among patients undergoing surgical resection, pCR was defined as the percentage of patients with no residual cancer cells in both the tumor bed and lymph nodes (ypT0N0) as assessed on the resection specimens. R0 resection rate was defined as the percentage of patients with tumor-free surgical margins. Overall survival (OS) was defined as the time from the first dose of camrelizumab to all-cause death. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AEs) version 5.0 (20). Surgical findings included postoperative complications, duration of hospital stay, and postoperative 90-day mortality.

Data collection

Data on patient demographic and clinical characteristics [e.g., age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index (BMI), tumor location, clinical stage, serum lactate dehydrogenase (LDH) level], treatment, pathological and surgical findings (e.g., pCR, R0 resection rate), and safety were prospectively collected from the electronic medical records, radiological reports, pathological reports, laboratory results, and operative notes. The patients were followed-up according to routine clinical practice when possible. All data were cross-checked for accuracy and consistency. The pathological findings were ascertained from the pathological reports. Any missing or inconsistent data were double-checked and confirmed by medical staff.

Statistical analysis

The pCR was analyzed in patients who underwent surgery. The analysis for OS and safety was performed in patients who received at least 1 dose of the study drug. All statistical analysis was descriptive. Continuous variables were presented with mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were presented with frequency and percentage. The 95% confidence interval (CI) was estimated for dichotomous outcomes (e.g., pCR) using the Clopper-Pearson method. OS curves and rates were estimated using the Kaplan-Meier (KM) methods. Univariate and multivariate logistic regression analysis was performed to identify potential factors for predicting a pCR of patients. The odds ratios (ORs) and corresponding 95% CIs were provided. All statistical analysis was performed with the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between June 1, 2020 and July 13, 2022, a total of 255 patients were enrolled and included in this analysis. The median age of participants was 64 (range, 27 to 82) years, with almost half of (46.2%) them aged 65 years or older. Most participants were male (82.0%) and had no smoking history (61.6%). More than half (52.9%) of the participants were recorded to have normal weight at baseline. Most tumors were located at the middle thoracic esophagus (71.0%) and classified as clinical stage III–IVA (82.4%). Overall, 31 (12.2%) participants had increased serum LDH levels. The baseline patient characteristics are summarized in *Table 1*.

Table 1 Patient characteristics

Variables	Value (n=255)
Age (years)	
Median [range]	64 [27, 82]
≥65, n (%)	118 (46.3)
Sex, n (%)	
Male	209 (82.0)
Female	46 (18.0)
ECOG PS, n (%)	
0	192 (75.3)
1	62 (24.3)
Unknown	1 (0.4)
BMI (kg/m^2)	
Mean ± SD	21.0±3.0
<18.5, n (%)	39 (15.3)
18.5–24.9, n (%)	135 (52.9)
25.0–29.9, n (%)	23 (9.0)
Unknown, n (%)	58 (22.7)
Tumor location[†], n (%)	
Upper	28 (11.0)
Middle	181 (71.0)
Lower	46 (18.0)
Smoking history, n (%)	
Yes	98 (38.4)
No	157 (61.6)
Clinical T stage, n (%)	
Tx	2 (0.8)
T1	3 (1.2)
T2	11 (4.3)
T3	197 (77.3)
T4	35 (13.7)
Unknown	7 (2.7)
Clinical N stage, n (%)	
Nx	31 (12.2)
N0	14 (5.5)
N1	85 (33.3)
N2	100 (39.2)
N3	18 (7.1)
Unknown	7 (2.7)
cTNM stage, n (%)	
I	3 (1.2)
II	34 (13.3)
III	159 (62.4)
IVA	51 (20.0)
Unknown	8 (3.1)
LDH level[‡], n (%)	
Normal (LLN, ULN)	204 (80.0)
Increased (>ULN)	31 (12.2)
Decreased (<LLN)	4 (1.6)
Unknown	16 (6.3)

[†], one patient had separate tumors located at both the middle and lower thoracic esophagus; [‡], values for the normal range (LLN, ULN) vary slightly among clinical laboratories. ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; SD, standard deviation; cTNM, clinical tumor-node-metastasis; LDH, lactate dehydrogenase; ULN, upper limit of normal; LLN, lower limit of normal.

Treatments

All participants received at least one dose of camrelizumab-containing neoadjuvant therapy. The median number of cycles administered was 2, ranging from 1 to 6. Almost all (98.8%) participants received neoadjuvant therapy with camrelizumab plus chemotherapy. Chemotherapy with nab-/paclitaxel and platinum was most commonly prescribed among patients receiving camrelizumab plus chemotherapy (*Table 2*); 3 patients received camrelizumab monotherapy, all of whom received less than 3 cycles.

Of the 255 patients, 169 (66.3%) underwent surgical resection. From the 86 patients who did not have surgery at the data cutoff date, 30 (37.0%) chose to not undergo surgery. The other reasons included progressive disease, systemic therapy AEs, being medically ineligible for surgery because of older age or poor performance, and death (1 patient committed suicide). Among the 169 resected patients, 84 (49.7%) underwent Ivor-Lewis esophagectomy, 76 (45.0%) McKeown esophagectomy, and 4 (2.4%) received Sweet esophagectomy. Most (89.9%) patients completed the procedures through a minimally-invasive approach. Three patients had a conversion to conventional procedure. The median interval from the end of camrelizumab treatment to surgery was 37 (IQR,

Table 2 Treatments

Variables	Value (n=255)
Number of cycles of neoadjuvant therapy	
Median [range]	2 [1, 6]
1	7 (2.7)
2	196 (76.9)
3	35 (13.7)
4	12 (4.7)
5	2 (0.8)
6	3 (1.2)
Treatment pattern, n (%)	
Camrelizumab monotherapy	3 (1.2)
Camrelizumab plus chemotherapy	252 (98.8)
Nab-paclitaxel plus platinum	231 (91.7)
Paclitaxel plus platinum	14 (5.6)
Fluorouracil plus platinum	7 (2.8)
Number of patients undergoing surgery	169 (66.3)
Interval to surgery (days), median [IQR]	37 [31, 43]
≥5 weeks, n (%)	100 (59.2)
<5 weeks, n (%)	63 (37.3)
Unknown, n (%)	6 (3.6)
Postoperative adjuvant therapy, n (%)	86 (50.9)
Immunotherapy plus chemotherapy	56 (65.1)
Immunotherapy	12 (14.0)
Chemotherapy	12 (14.0)
Chemoradiotherapy	3 (3.5)
Radiation therapy	1 (1.2)
Unknown	2 (2.3)

IQR, interquartile range.

Table 3 Pathological and surgical findings

Variables	Value (n=169)
R0 resection, n (%)	146 (86.4)
pCR	
N (%)	36 (21.3)
95% CI (%)	15.4, 28.3
ypT stage, n (%)	
0	14 (8.3)
1	20 (11.8)
2	27 (16.0)
3	46 (27.2)
4a	8 (4.7)
4b	2 (1.2)
Unknown	52 (30.8)
ypN stage, n (%)	
0	55 (32.5)
1	33 (19.5)
2	21 (12.4)
3	7 (4.1)
Unknown	53 (31.4)
Surgical outcomes	
Operation time (hours), median [IQR]	5.0 [4.5, 6.0]
Intraoperative blood loss (mL), median [IQR]	100 [100, 200]
Duration of postoperative hospital stays (days), median [IQR]	12 [9, 14]
Perioperative complications, n (%)	76 (45.0)
Postoperative 30-day mortality, n (%)	0 (0.0)
Postoperative 90-day mortality, n (%)	2 (1.2)

pCR, pathological complete response; CI, confidence interval; yp, pathological; IQR, interquartile range.

31 to 43) days. Almost half (86/169) of the patients who underwent surgery were recorded to receive postoperative adjuvant therapy, with immunotherapy plus chemotherapy (65.1%) being most commonly prescribed, followed by immunotherapy alone (14.0%) and chemotherapy alone (14.0%) (*Table 2*).

Pathological and surgical findings

Of the 169 resected patients, 146 (86.4%) achieved R0 resection [6 (3.6%) R1 resection and 17 (10.0%) unknown for resection status] and 36 (21.3%) achieved pCR (*Table 3*). Patients receiving 3 or more cycles of camrelizumab benefitted more than those receiving 2 or less cycles in terms of the pCR rate (34.6% *vs.* 18.9%, P=0.025). The data cutoff date of October 24, 2022, the median follow-up time was 12.9 (IQR, 6.9 to 19.2) months. The median OS was not yet reached. The estimated 1-year OS rate was 87.8% (95% CI: 82.5–91.5%) (*Figure 1*).

Multivariate logistic regression analysis showed that

older age (≥65 *vs.* <65 years: OR: 3.20; 95% CI: 1.08–9.55; P=0.037) and increasing cycles of neoadjuvant therapy (>2 *vs.* ≤2 cycles: OR: 4.52; 95% CI: 1.21–16.91; P=0.025) were independently associated with a better pCR (*Table 4*).

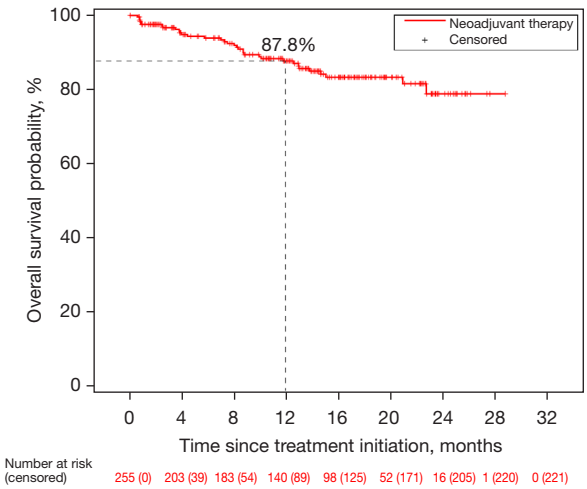

Figure 1 KM analysis of OS of patients. KM, Kaplan-Meier; OS, overall survival.

The median operation time was 5.0 (IQR, 4.5 to 6.0) hours. The estimated median intraoperative blood loss was 100 (IQR, 100 to 200) mL. A total of 76 (45.0%) patients developed postoperative complications. The most common postoperative complications were infectious pneumonia (27.8%), incision pain (11.2%), and pleural effusion (8.9%). The median duration of postoperative hospital stay was 12 (IQR, 9 to 14) days. There were 2 (1.2%) patients who died within 90 days postoperatively, 1 due to postoperative upper gastrointestinal bleeding and the other due to postoperative anastomotic leakage.

Safety

AEs of any grade were documented in almost all (99.6%) participants, most commonly nausea (60.8%), hypokalemia (49.8%), and anemia (40.4%). Grades 3–5 AEs were observed in 14.5% of participants. Reactive cutaneous capillary endothelial proliferation, a camrelizumab-specific AE, occurred in 100 (39.2%) participants, and cases were mild (all were grade 1 or 2). The treatment-emergent AEs occurring in ≥5% of the participants are shown in *Table 5*.

Table 4 Univariate and multivariate logistic regression analysis of pCR

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (≥65 *vs.* <65 years)	2.37 (0.95, 5.88)	0.063	3.20 (1.08, 9.55)	0.037
Sex (female *vs.* male)	1.87 (0.62, 5.63)	0.267	1.84 (0.44, 7.65)	0.403
ECOG PS (1 *vs.* 0)	0.19 (0.02, 1.51)	0.116	0.11 (0.01, 1.08)	0.058
BMI (*vs.* <18.5 kg/m^2)				
18.5–24.9 kg/m^2	0.44 (0.11, 1.68)	0.179	0.31 (0.06, 1.70)	0.177
25.0–29.9 kg/m^2	0.73 (0.15, 3.65)	0.878	0.50 (0.07, 3.51)	0.874
Tumor location (*vs.* upper)				
Middle	1.58 (0.31, 7.94)	0.311	1.51 (0.21, 10.74)	0.452
Lower	0.79 (0.11, 5.66)	0.540	0.84 (0.08, 8.63)	0.660
Smoking history (yes *vs.* no)	0.81 (0.32, 2.05)	0.657	1.06 (0.34, 3.33)	0.914
cTNM stage (III–IVA *vs.* I–II)	2.75 (0.59, 12.87)	0.200	2.24 (0.42, 12.04)	0.346
Increased LDH levels (yes *vs.* no)	0.47 (0.10, 2.23)	0.341	0.67 (0.11, 3.96)	0.657
Treatment cycles (>2 *vs.* ≤2)	3.20 (1.05, 9.74)	0.041	4.52 (1.21, 16.91)	0.025
Time interval to surgery (≥5 *vs.* <5 weeks)	1.27 (0.49, 3.28)	0.626	1.09 (0.36, 3.33)	0.874

pCR, pathological complete response; OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; cTNM, clinical tumor-node-metastasis; LDH, lactate dehydrogenase.

Table 5 AEs occurring in ≥5% of participants

AEs	Grade 3–5	Any grade
Total	37 (14.5)	254 (99.6)
Nausea	7 (2.7)	155 (60.8)
Hypokalemia	7 (2.7)	127 (49.8)
Anemia	6 (2.4)	103 (40.4)
Reactive cutaneous capillary endothelial proliferation	0	100 (39.2)
Hypoproteinemia	3 (1.2)	93 (36.5)
Infectious pneumonia	6 (2.4)	74 (29.0)
White blood cell decreased	3 (1.2)	58 (22.7)
Cough	1 (0.4)	50 (19.6)
Abnormal percentage of eosinophils	1 (0.4)	43 (16.9)
Vomiting	0	39 (15.3)
Diarrhea	1 (0.4)	36 (14.1)
Hyperuricemia	1 (0.4)	33 (12.9)
Myelosuppression	6 (2.4)	30 (11.8)
Electrolyte imbalance	0	28 (11.0)
Abnormal liver function	0	25 (9.8)
Pleural effusion	0	20 (7.8)
Blood LDH increased	0	19 (7.5)
Fever	0	17 (6.7)
Productive cough	0	17 (6.7)
Platelet count decreased	3 (1.2)	16 (6.3)
Neutrophil count decreased	2 (0.8)	16 (6.3)
Sinus bradycardia	0	15 (5.9)

Data are presented as n (%). AE, adverse event; LDH, lactate dehydrogenase.

Discussion

In this prospective multicenter observational cohort study, we investigated the efficacy and safety of camrelizumab-containing neoadjuvant therapy in patients with locally advanced ESCC. The percentage of patients achieving a pCR (21.3%) was generally within the range of 0% to 44% reported for neoadjuvant immunotherapy plus chemotherapy studies (15,16,18,21-23). In a multicenter single-arm study of camrelizumab plus nab-paclitaxel and carboplatin (NICE regimen), 20 (39.2%) patients achieved a pCR among the 51 patients who underwent surgery for locally advanced ESCC (12). Meanwhile, two single-arm studies reported a pCR rate of 21.6% and 25% with the NICE regimen in patients with resectable ESCC, respectively (14,24). Several studies have explored the therapeutic effects of other chemotherapeutic regimens (nab-paclitaxel and cisplatin, docetaxel and carboplatin, nab-paclitaxel and nedaplatin) in the camrelizumab combination settings. The percentage of patients achieving a pCR varied from 20% to 41.7% (13,25,26). Notably, 2 cycles of treatment were scheduled in all the aforementioned studies. A recent study investigated the therapeutic effects of 3 cycles of neoadjuvant camrelizumab plus chemotherapy (nab-paclitaxel and capecitabine) in locally advanced ESCC, and a pCR rate of 33.3% was achieved (27). In a recent systematic review and meta-analysis, a numerically higher pCR rate was observed in patients receiving paclitaxel plus cisplatin or carboplatin regimens when compared with the other chemotherapy regimens (30% *vs.* 21%) in the immunotherapy combination settings. Furthermore, a numerically higher pCR rate was noted in patients receiving 3 or 4 cycles than those receiving 2 cycles (32.0% *vs.* 23.7%), although this did not reach statistical significance (P=0.30) (21). Similar results were noted in a recent real-world study of neoadjuvant immune checkpoint inhibitors in patients with EC (23). In the present study, almost all (98.8%) participants received neoadjuvant camrelizumab in combination with chemotherapy, with the nab/paclitaxel plus platinum agents being most commonly used. The median number of treatment cycles was 2, ranging from 1 to 6. Additionally, patients receiving 3 or more cycles of treatment seemed to benefit more than those receiving 2 or less cycles in terms of the pCR rate (34.6% *vs.* 18.9%). Older age and increasing cycles of neoadjuvant camrelizumab therapy were identified as independent predictors for pCR. These results were partially consistent with previous findings, which indicated that elder age and clinical T stage, but not treatment cycles, were independent factors (23). Two to 4 treatment cycles have been recommended for neoadjuvant immunotherapy plus chemotherapy in the local guideline (28). The optimal strategies (e.g., combination, duration) for neoadjuvant therapy need to be explored in the immunotherapy era to guide clinical practice.

Neoadjuvant therapy with camreliuzmab-containing regimens was generally well tolerated. The safety profile observed in this study was consistent with that of previous reports (21,29). Grade 3–5 AEs occurred in approximately

15% of participants, with nausea, hypokalemia, and anemia, which typically occur with chemotherapy, being most frequent. Reactive cutaneous capillary endothelial proliferation was recorded in 39.2% of participants, and all cases were mild, corroborating the findings of previous studies (12,14-16). However, the number of patients undergoing surgical resection was comparatively smaller in this study, as more than one-third of patients not undergoing surgery chose so of their own volition. The surgical findings were generally consistent with those reported in previous studies (12-14,25-27,30). Postoperative complications occurred in 45.0% of the resected patients, which was within the range of 26.3% to 47.1% reported in previous studies of neoadjuvant camrelizumab therapies (12,13,16,31). The findings of this study, together with other studies, support the feasibility and translation of the trials' results of camrelizumab-containing neoadjuvant therapy into routine clinical practice.

The main strength of this study is the prospective nature of the study design and the comparatively large sample size. The key limitation of this study is the relatively short follow-up time, thus not allowing for a comprehensive report on tumor recurrence/progression or survival. The long-term efficacy of camrelizumab-containing neoadjuvant therapy in patients with ESCC needs to be studied further. Besides, PD-L1 expression was not mandatory and, therefore, not routinely tested in clinical practice. Also, the immune-related AEs were not routinely documented in clinical practice. Additionally, missing data in the observational study may introduce potential biases (e.g., R0 resection). Future studies of the potential prognostic value of PD-L1 expression are required. Nevertheless, this study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC.

Conclusions

Camrelizumab-containing neoadjuvant therapy showed acceptable effectiveness and safety profiles in real-life ESCC patients. This study validated the feasibility of neoadjuvant camrelizumab therapy for ESCC in daily practice.

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Footnote

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Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1408/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1408/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the China Ethics Committee of Registering Clinical Trials (No. ChiECRCT20200264) and the Institutional Review Board of Zhangzhou Hospital Affiliated to Fujian Medical University (No. 2022LWB127) and informed consent was provided by all individual participants.

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