Neoadjuvant sintilimab and chemotherapy for resectable esophageal squamous cell carcinoma: a prospective, single-arm, phase II study

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Research Article

Keywords: Esophageal squamous cell carcinoma, Neoadjuvant therapy, Sintilimab, Chemotherapy.

Posted Date: November 7th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3538085/v1

Abstract

Background: Combining PD-1 blockade with chemotherapy has widely used in first line treatment of metastatic esophageal squamous cell carcinoma (ESCC). However, their efficacy as neoadjuvant therapy in resectable ESCC is little known. This study was performed to assess the activity and safety profile of the combination of sintilimab and chemotherapy in the neoadjuvant treatment of ESCC.

Methods: In this single-arm, phase II study, we recruited patients with histopathologically diagnosed resectable ESCC who had clinical cT1-3/N0-1M0 (stage II-). Patients were given sintilimab (200mg, iv, d1) in combined with chemotherapy (nab-paclitaxel 260 mg/m^2, d1 and cisplatin 75 mg/m^2, d1-3) every 3 weeks for 2 cycles. The primary endpoint was pathological complete response (pCR).

Results Between Nov 2020 and Nov 2022, 29 patients were enrolled and 27 patients completed the two cycles of neoadjuvant therapy. A total of 21 patients underwent surgery without treatment-related surgical delay. The major pathologic response (MPR) rate was 42.9% (9/21) and the pathologic complete response (pCR) rate was 28.6% (6/21). The most frequent grade 3 or 4 treatment-related adverse events (TRAE) were leukopenia (26.7%), neutropenia (20%) and pneumonia (6.7%). There was no surgical delays or unexpected surgical complications related to drug toxicity.

Conclusions: The combination of sintilimab and chemotherapy shows an encouraging pCR rate and a favorable safety profile in this study, which indicated this treatment regimen may become an alternative option in the neoadjuvant treatment of resectable esophageal squamous cell carcinoma, especially for Chinese patients.

Introduction

Esophageal cancer is the seventh most frequently diagnosed cancer and the sixth leading cause of cancer related deaths globally [1]. The incidence of esophageal cancers shows geographic variation and china belongs to the highest-incidence area. In 2016, 252500 new cases esophageal cancer were diagnosed and 193900 patients had died caused by esophageal cancer in China [2]. Squamous cell carcinoma (SCC) is the predominant histological subtype in China, accounting for about 90% of new diagnosed EC.

Esophagectomy is the most important curable treatment for resectable esophageal squamous cell carcinoma (ESCC). Neoadjuvant chemotherapy and chemoradiation are widely adopted as the standard preoperative treatment to improve the R0 resection rate and, subsequently, long term survival [3]. In OEO2 study, neoadjuvant chemotherapy with cisplatin and fluorouracil moderately increased the R0 resection rate from 54–60% and decreased the risk of death and disease progression by 16% and 18% compared with surgery only for patients with ESCC [4, 5].

Addition of radiotherapy to neoadjuvant chemotherapy seems to further enhance the treatment efficacy. CROSS study showed preoperative chemoradiation with carboplatin and paclitaxel decreased the risk of

death and disease progression by both 52% compared with surgery only. The R0 resection rate reached 92% and the pathological complete response was 29% [6].

However, neoadjuvant chemoradiotherapy tends to cause more postoperative complications, which leads to poor tolerance and limits the survival benefit. A randomized clinical trial indicated addition of radiotherapy to neoadjuvant chemotherapy results in higher histological complete response rate, higher R0 resection rate, but, had no significantly affect to PFS and OS [7]. In fact, the preoperative chemotherapy was more widely used in China since its better tolerance and lower economic burden. Thus, there is an urgent need for new neoadjuvant treatments which have higher pathological response rate, better tolerance and can further improve the survival outcomes.

The combination of immune checkpoint inhibitor such as anti-PD-1 monoclonal antibody with platinum-based chemotherapy has become the standard first-line treatment for ESCC. Sintilimab is a novel fully recombinant human IgG4 anti-PD-1 monoclonal antibody. In a randomized phase 3 study (ORIENT-15 study), sintilimab plus chemotherapy showed significant improves in survival benefit and tumor response in the first line treatment of ESCC compared with placebo. The median progression free survival was prolonged from 5.7months to 7.2 months (HR = 0.56, $p < 0.001$). The ORR was elevated from 45–66%. The safety profile of two treatment regimens were similar [8]. These results demonstrated the synergy and feasibility for the regimen of sintilimab plus chemotherapy in the ESCC. This open, single-arm pilot study was performed to explore the efficacy and safety of neoadjuvant sintilimab combined with chemotherapy in the resectable ESCC.

Patients and methods

Patients

Eligible patients were 18–70 years old and diagnosed as having histopathologically confirmed ESCC of clinical stage II/III/IVA. The disease was deemed to be surgically resectable or potentially resectable by thoracic surgeon. Other key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function and no history of other malignant tumors. No prior chemotherapy, radiotherapy or immune checkpoint inhibitor were permitted. Patients who existed or had the risk of developing tracheoesophageal fistula or aortoesophageal fistula were also excluded.

Study design

This is a single-arm, phase II, perspective study. Eligible patients were infused with nab-paclitaxel (260 mg/m^2, d1), cisplatin (25 mg/m^2, d1-3) and sintilimab (200mg d1) intravenously every 3 weeks for totally two cycles before surgery. After about 4–6 weeks of the last dose for neoadjuvant therapy, esophagectomy (McKeown esophagogastrectomy or thoracoscopic McKeown esophagogastrectomy) was performed. Postoperative treatment was allowed and decided by the investor. The dose interrupted, delayed, or discontinued of sintilimab was recommended when some grade 3 or 4 AEs occurred while the dose reduction was not allowed. For chemotherapy, the dose can be reduced in the events of some high

grade hematology or non-hematology toxicities. This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan Polytechnic University (KY2020-11-001). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines. All enrolled patients provided written informed consent. The trial was registered in chictr.org.cn, number ChiCTR2000040345

Outcomes

The primary endpoint was pathologic complete response (pCR). The key secondary endpoints included major pathologic remission (MPR) and objective response rate (ORR). The secondary endpoints included major pathological remission (MPR), objective response rate (ORR), and safety.

Pathologic response was measured using the modified Ryan scheme in the College of American Pathologists (CAP) Cancer Protocol for Esophageal Carcinoma. Tumor regression grade (TRG) was classified in four grades. 0 (Complete response): no viable cancer cells, including lymph nodes; 1 (near complete response): single cells or rare small groups of cancer cells; 2 (partial response): residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells; 3 (poor or no response): extensive residual cancer with no evident tumor regression [1]. The pCR was defined as the TRG 0 and the MRP was defined as the sum of pathologic complete response and near pathologic complete response (TRG 0 ~ 1). Pathological regression was assessed using hematoxylin and eosin (H&E) stained slides of surgical specimens and both primary tumor and sampled lymph nodes were evaluated.

ORR was calculated as the sum of patients who achieved tumor complete response (CR) and partial response (PR) according to RECIST 1.1. Tumor response was evaluated based on enhanced CT scan images before and after the completion of neoadjuvant treatment (7 days before surgery). Radiographic surveillance was continued every 90 days till disease recurrence/progression or death. All pathological data and imaging data were reviewed by two independent pathologists or radiologists. Treatment-related adverse events (TRAEs) and abnormal laboratory findings were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

The sample size was calculated by PASS version 15. The pCR of primary esophagus after chemotherapy was approximately 10%. Assuming that the neoadjuvant sintilimab plus nab-paclitaxel-cisplatin regimen would achieve a pCR rate of 30%, a sample size of 24 was required to provide 80% power, calculated using the one-proportion exact-test with a one-sided type I error of 5%. Considering a dropout rate of 15%, we planned to enroll 29 patients. Pathologic response was estimated based on the population who received surgery. The safety set included all patients who received at least one dose of treatment combination. All statistical analyses were performed using SAS 9.4 statistical analysis software.

Results

Between Nov 2020 and Nov 2022, 35 patients were screened and 29 were enrolled. As shown in Table 1. 20 patients were males and 9 were females. The median age was 64.5 years (range, 35–70 years). The most common locations of the primary tumor were the middle third esophagus (65.5%), followed by lower esophagus (27.6%). Only 2 patients (6.9%) had the primary tumor in the upper esophagus. At baseline, 4 patients (13.8%) had AJCC Eighth Edition-defined stage B disease while the other had disease of stage A (31.0%) or III (55.2%).

Table 1
Patient demographic and baseline characteristics

Characteristics	N = 29
Age(year, range)	64 (35–70)
Gender, n (%)	
Male	20 (69.0)
Female	9 (31.0)
Performance score, n (%)	
0	25 (86.2)
1	4 (13.8)
Tumor location, n (%)	
Upper	2 (6.9)
Middle	19 (65.5)
Lower	8 (27.6)
Smoking history, n [%]	20 (69.0)
Drinking history, n [%]	18 (62.1)
Diabetes, n [%]	10 (34.5)
Hypertension, n [%]	8 (27.6)
Tumor	
T1	9
T2	4
T3	16
Node	
N0	8
N1	21
Clinical TNM stage*, n (%)	
II	13 (44.8)
III	16 (55.2)
*Clinical disease stage was assessed according to the criteria of the American Joint Committee on Cancer, Eighth Edition.	

27 patients completed the two cycles of neoadjuvant therapy and the other two were lost follow up after the first dose of regimen. Totally 21 patients (72.4%) received radical resection and 6 patients refused surgery. One patient, who had immune-associated pneumonia and recovered after glucocorticoid treatment, withdrew from the study and continued chemotherapy due to concerns about the risk after surgery. Two patients who achieved radiographic complete response decided not to receive surgery by their own choice. Three patients refused to receive surgery in this institution and withdrew the informed consent. No treatment-related surgical delay occurred and the median interval between the last dose of neoadjuvant therapy and surgery was 32 days (range: 28.5, 41.5). All patients received minimally invasive esophagectomy and achieved R0 surgical resection. No death or unplanned hospital readmission occurred within 3 months after surgery. The operation information was summarized in Table 3.

Table 2
Treatment-Related Adverse Events

TRAE	Incidence, n (%)	
	All grades	Grade 3 ~ 4
Alopecia	19 (65.5)	
Fatigue	18 (62.1)	
Leukopenia	17 (58.6)	8 (27.6)
Neutropenia	17 (58.6)	6 (20.7)
Nausea	12 (41.4)	
Increased alanine transaminase	7 (24.1)	
Diarrhea	6 (20.7)	
Vomiting	6 (20.7)	
Increased aspartate transaminas	6 (20.7)	
Anemia	5 (17.2)	
Thrombocytopenia	5 (17.2)	1 (3.4)
Rash	4 (13.8)	
Hypothyroidism	3 (10.3)	
Pneumonia	2 (6.9)	1 (3.4)

Table 3
Operation information and postoperative complications

Characteristics	
Operation information	
Interval to surgery (days)	32.0 (28.5, 41.5)
Duration of operation (min)	230.0 (210.0, 432.0)
Intraoperative blood loss (mL)	125.0 ± 34.7
Lymphadenectomy	
Two-field	14 (65.8%)
Three-field	7 (34.2%)
Surgical approach	
MIE	21 (100%)
OE	0
Postoperative complications	
Anastomotic leakage	4 (18.5%)
pneumonia	2 (11.1%)
pleural effusion	3 (14.8%)

For 21 patients who received surgery, 6 (28.6%) reached pathologic complete response (pCR), 3 (14.3%) had near pathologic complete response, achieved a major pathologic response (MPR) rate of 42.9%. Tumor regression score of the rest 12 patients was 2.

Radiographic evaluation was performed in 24 patients after 2 cycles of treatment. Tumor shrinkage was observed in all patients. According to RECIST v1.1, 4 patients (16.7%) achieved complete response (CR), 13 (54.2%) achieved partial response (PR), and the rest 7 patients (29.2%) were evaluated as stable disease (SD). Overall, the objective response rate (ORR) and disease control rate (DCR) was 70.8% and 100%, respectively.

All patients experienced at least one adverse event (Table 2) and the treatment related adverse events (TRAEs) of any grade were observed in 25 (86.2%) patients. The most common chemotherapy related AEs of all grades were alopecia (65.5%), leukopenia (58.6%), neutropenia (58.6%) and the most common immune-related AEs were hypothyroidism (10.8%), pneumonia (6.9%). Nine patients suffered grade 3 AEs, which were all identified as treatment-related. Chemotherapy related grade 3 or 4 AEs included leukopenia (27.6%), neutropenia (20.7%) and thrombocytopenia (3.4%). One patients experienced immune-

associated pneumonia of grade 3 after 2 cycles of the treatment and the recovered by the treatment of glucocorticoid. No other grade 3 or 4 irAE occurred. No patient died in-hospital or within 3 months after surgery and no severe perioperative complications occurred. Six patients needed chemotherapy suspension because of haematological toxicities and 4 were given lower dose of nab-paclitaxel (200 mg/m^2, d1) and cisplatin (20 mg/m^2, d1-3) in the subsequent cycle. No treatment-related surgical delays occurred.

The postoperative complications were summarized in Table 3. No patient died in-hospital or within 3 months after surgery and no unexpected surgical complications were observed. The most common complications were anastomotic leakage (4 patients, 19.0%) and pleural effusion (3 patients, 14.3%). All patients recovered after non-surgical intervention. Two patients (9.5%) developed postoperative pulmonary infection and one deteriorated into sepsis. Both patients recovered after the infusion of broad-spectrum antibiotics. Recurrent laryngeal nerve paralysis was observed in two patients (9.5%).

Discussion

In this prospective, single-arm pilot study, neoadjuvant treatment with sintilimab and chemotherapy (Nab-paclitaxel 260 mg/m^2, d1 and cisplatin 75 mg/m^2, d1-3) for 2 cycles in the resectable ESCC resulted in a pCR rate of 28.6% and MPR rate of 42.9%. The radiographic complete response rate according to RECIST 1.1 was 16.7%. No surgical delays or mortality within 3 months after surgery occurred. Eight (38.1%) patients developed surgical complications and all recovered by non-surgical interventions. These results preliminarily disclosed the efficacy and safety of our treatment regimen in neoadjuvant treatment of resectable ESCC.

The prognostic significance of pathologic complete response (pCR) after induction therapy in patients with esophageal cancer has been demonstrated in several studies [9, 10]. The pCR and MPR rates of our study were 28.6% and 42.9%. Since two patients with radiographic complete response and one patient with radiographic partial response did not receive surgery and the data of their pathologic response was lost, the real pCR and MPR rate of our treatment regimen may further increased. As we expected, in addition of immune checkpoint inhibitor to chemotherapy obviously elevated the pCR rate compared with preoperative chemotherapy [11].

The CROSS study promote the concurrent chemoradiotherapy to become the standard neoadjuvant therapy for resectable ESCC. Neoadjuvant concurrent chemoradiotherapy can achieve higher pCR rate compared with neoadjuvant chemotherapy and was widely adopted in western countries. However, its accessibility and affordability is poor in same area of China. In our study, the pCR rate was comparable with CROSS study (28.6% vs. 29%), indicated neoadjuvant therapy with the immune checkpoint inhibitor and chemotherapy can be a possible alternative. Another advantage of neoadjuvant chemotherapy is tis favorable safety profile. Radiotherapy may increase the incidence and severity of some AEs such as leukopenia, neutropenia and radiation esophagitis. In NEOCRTEC5010 study, the incidence of grade 3 / 4 leukopenia and neutropenia was 31.8% / 17.0% and 23.3% / 22.4%, respectively, while in our study, the

incidence of grade 3 leukopenia and neutropenia was 27.6% and 20.7%. and only 3 patients occurred grade 4 haematological AEs. In the aspect of postoperative complications, our study arose two cases (9.5%) of respiratory complication and 4 cases (19.0%) of anastomotic leakage occurred while all patients recovered after non-surgical intervention. No patient died in hospital or within 90 days after surgery. Perioperative complication and treatment-related death will impair the survival benefit of the neoadjuvant. A randomized clinical trial involved 181 patients showed no significant PFS and OS benefit when adding radiotherapy to neoadjuvant although obviously higher histological complete response rate and higher R0 resection rate were observed. This phenomenon was mainly attributed to the relatively higher incidence of postoperative complication in the group of neoadjuvant chemoradiotherapy, especially anastomotic leakage and respiratory and more postoperative mortality events [7].

Nab-paclitaxel and cisplatin was deemed as a preferred chemotherapy regimen and widely used in China. Compared with CROSS study [12], high dose carboplatin (AUC = 2 per weeks) was replaced with moderated dose cisplatin in our study. In a multicenter, randomized clinical trial involved 321 patients in China to compare the efficacy and toxicity of paclitaxel with fluorouracil, cisplatin or carboplatin in the definitive chemoradiotherapy against esophageal squamous cell carcinoma (ESCC), cisplatin combined with paclitaxel showed the best 3-year OS rate although the toxicity was relatively higher [13].

In accord with other studies [14], the pathologic response was positively correlated with radiographic response. In patients who achieved pCR, two were evaluated as radiographic CR and 4 reached PR. In the rest 8 patients who had radiographic PR, 3 had near pathologic complete response (TGS1).

In terms of surgery, All 21 patients successfully underwent McKeown MIE without open surgery, the R0 resection rate reached 100%. Our mean operative time were 230 minutes. The intraoperative blood loss were 125.0 ± 34.7 mL (mean ± SD), comparable with the esophageal cancer without neoadjuvant treatment. All of this demonstrates that neoadjuvant sintilimab combined with chemotherapy does not increase the difficulty of surgery. At the same time, we found that after this neoadjuvant treatment, esophageal tumors tended to loosely adhere, and easier removal from surrounding tissue during operating. This appears to be different from patients after radiotherapy or neoadjuvant therapy for lung cancer. NEOSTAR trial (NCT03158129) suggests that due to hilar fibrosis in some patients, it is more difficult to separate the blood vessels. This indicated that different cancer types may cause different response to ICIs [15]. It also indicated that neoadjuvant sintilimab combined with chemotherapy did not increase the difficulty of the surgery.

This study has some limitations. First, it was an exploratory single-arm study with a small sample size. A randomized controlled study is warranted, especially to compare this regimen with standard neoadjuvant chemoradiotheray. Second, the duration of follow-up was limited and the data of survival was not mature. In addition, the predictive biomarkers will be explored in the further studies.

Conclusions

This prospective, single-arm, phase II study showed promising efficacy and favorable tolerability of neoadjuvant sintilimab and chemotherapy in the resectable esophageal squamous cell carcinoma. Encouraging pCR rate and tumor response were observed. These results primarily indicated that the combination of sintilimab and chemotherapy may become an alternative option in the neoadjuvant treatment of resectable esophageal squamous cell carcinoma.

Declarations

Acknowledgments

We thank the patients and their families, all caregivers, and the referring oncologists for technical help with the radiological reviews.

Funding

This work was partially supported by a grant from the Project of Science and Technology of Henan Province (2018020995).

Conflicts of interest

All authors declared that they have no conflicts of interest.

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