Original Article

Efficacy and safety of vinorelbine and cisplatin regimen of different doses and intensities for neoadjuvant chemotherapy in patients with locally advanced esophageal carcinoma

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Background: There are few studies focused on comparing the toxicity, postoperative complication rate, and survival among patients with locally advanced esophageal squamous cell cancer receiving a different dose and intensity of vinorelbine plus cisplatin for neoadjuvant chemoradiotherapy (nCRT) followed by surgery.

Methods: In total, 78 patients diagnosed with locally advanced esophageal squamous cell cancer that had received a vinorelbine and cisplatin (VP)1 or VP2 regimen for nCRT followed by surgery in Taizhou Hospital of Zhejiang Province between June 2008 and December 2016 were retrospectively analyzed. The VP1 regimen involved cisplatin 75 mg/m^2 on day 1, and vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles. The VP2 regimen involved cisplatin 25 mg/m^2 on days 1 to 4, and vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles. The rate of adverse events, postoperative complications, and survival were compared between the two groups.

Results: The median overall survival (OS) was 97.6 months (85.6–109.7) in the VP2 group, which was not significantly different to that of the VP1 group [hazard ratio (HR), 1.008 (0.999–1.108); P=0.509]. The main toxicity was hematologic adverse events. The VP2 group had significantly higher rates of all grades of anemia, leukopenia, neutropenia, and thrombocytopenia (all P<0.05), as well as grade 3 or 4 of leukopenia and neutropenia (P<0.05) compared to the VP1 group. Regarding postoperative complications, the VP2 group had a significantly higher rate of pulmonary infection than the VP1 group (P<0.05).

Conclusions: Compared with VP2, VP1 showed comparable efficacy in terms of survival, with less hematologic toxicity and postoperative pulmonary infection. Therefore, we recommended that VP1 over VP2 to be the optimized VP neoadjuvant chemotherapy regimen for locally advanced esophageal squamous cell cancer.

Keywords: Esophageal squamous cell cancer; neoadjuvant chemoradiotherapy (nCRT); surgery; chemotherapy regimen; overall survival (OS)

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Introduction

China has the highest incidence rate of esophageal cancer (EC) and largest number of EC patients anywhere in the world (1). Most newly diagnosed esophagus cancer patients present with locally advanced disease. For this patient population, surgery is the mainstay treatment choice (2). The addition of neoadjuvant chemoradiotherapy (nCRT) has also been a standard treatment for locally advanced EC in many regions to improve the outcome of EC treatment (3). Theoretically, nCRT could improve local symptoms, reduce micro-metastasis, and prolong survival (3-5), and is thus a promising EC treatment pattern. Significant efforts have been exerted for further exploration of this therapy modality. However, nCRT-related toxicity and increased postoperative complications and mortality might be major problems that would limit the benefit of nCRT (6). Patients with esophageal squamous cell carcinoma (ESCC), and particularly those with advanced disease, tend to be poorly tolerant to chemotherapy due to the heavy use of tobacco and alcohol (6). In some studies, the chemotherapy-toxicity related deaths rates reached 10–14% among ESCC patients (7,8). According to the meta-analysis by Fiorica *et al.*, nCRT plus surgery increased postoperative mortality [odds ratio (OR) 2.10; P=0.01] compared with surgery alone (9). In one randomized study among EC patients, cisplatin-5-fluorouracil (FU) for eight cycles conferred no benefits on survival, but had more complications compared to no chemotherapy (10). Therefore, optimizing the dose and intensity, especially with regards to toxicity, is crucial in nCRT for ESCC.

The cisplatin-based chemotherapy regimen is the most often used regimen in EC treatment (11). Different combinations of platinum compounds and other chemotherapy agents had been examined in EC treatment (12). Vinorelbine is a semisynthetic vinca alkaloid that exhibits activity and low toxicity in ESCC treatment (13-15). When vinorelbine was combined with cisplatin, the two agents acted synergistically and showed superior tolerance and efficacy. In a study by Conroy *et al.*, the combination of vinorelbine and cisplatin (VP) was used to treat 71 metastatic ESCC patients. The response rate of the regimen was 33.8%, and the median survival was 6.8 months (6). VP neoadjuvant chemotherapy was extensively acknowledged to be sensitive for EC (16-19). Liu *et al.* compared VP and cisplatin/FU for neoadjuvant chemotherapy in 114 patients with locally advanced ESCC in a retrospective matched case-control study. In their study, the median overall survival (OS) in patients treated with cisplatin/vinorelbine was 52.8 months, which was significantly longer than that of the cisplatin/FU group (25.2 months) (20). However, the pattern of VP neoadjuvant chemotherapy administration varies in hospitals in China, and its optimal dose and intensity in terms of toxicity and efficacy has not yet been determined. VP1 (cisplatin 75 mg/m^2 on day 1; vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles) (17,18,20) and VP2 (cisplatin 25 mg/m^2 on days 1 to 4; vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles) (19) are two commonly used VP regimens for neoadjuvant chemotherapy in ESCC treatment. In order to optimize the dose and intensity of VP neoadjuvant chemotherapy for ESCC, we retrospectively compared the toxicity, postoperative complication rate, and survival among patients with locally advanced ESCC who received either the VP1 or VP2 regimen as neoadjuvant chemotherapy.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-458).

Methods

Patients

Between June 2008 and December 2016, 78 patients with locally advanced esophageal squamous cell cancer who had received VP1 or VP2 for nCRT followed by surgery in Taizhou Hospital of Zhejiang Province were retrospectively reviewed (*Table 1*).

The inclusion criteria were as follows: (I) patients with histologically confirmed resectable stage IIB or III thoracic ESCC (according to the 6th American Joint Committee on Cancer edition); (II) patients who had not received previous treatment; (III) patients who were expected to have at least 6 months survival; (IV) patients aged between 18 and 70 years; (V) patients with adequate marrow function: white blood cell ≥4.0×10^9/L, neutrophil ≥1.5×10^9/L, platelet ≥100.0×10^9/L, and hemoglobin ≥90 g/L; (VI) patients with normal liver and kidney function; (VII) patients with a Karnofsky performance score ≥90; (VIII) complete clinical data were available. The exclusion criteria were as follows: (I) patients who had received prior treatment for primary tumor or nodes; (II) patients with a history of or concomitant hemorrhagic diseases; (III) pregnancy or lactation; (IV) patients with peripheral neuropathy and the Common Terminology Criteria for Adverse Events, CTCAE v3.0 grade ≥2; (V) patients with prior malignancies, except for adequately treated basal or squamous cell skin

Table 1 Clinical characteristics of patients receiving different VP regimens

Characteristic	VP1 regimen (n=47)	VP2 regimen (n=31)	P value
Age, years	54.02±7.18	55.94±6.07	0.968
Gender			0.153
Male	42 (89.4)	24 (77.4)	
Female	5 (10.6)	7 (22.6)	
BMI, kg/m^2	22.34±3.4	22.69±3.35	0.193
KPS			1.000
90	47 (100.0)	31 (100.0)	
100	0 (0)	0 (0)	
Tumor location			0.112
Proximal third	5 (10.6)	4 (12.9)	
Middle third	29 (61.7)	22 (71.0)	
Distal third	13 (27.3)	5 (16.1)	
Clinical T stage			0.757
cT1-T2	2 (4.3)	5 (16.1)	
cT3	22 (46.8)	21 (67.8)	
cT4	23 (48.9)	5 (16.1)	
Clinical N stage			0.998
N0	22 (46.8)	0 (0)	
N1	25 (53.2)	31 (100.0)	
Clinical stage			0.361
IIB	2 (4.3)	5 (16.1)	
III	45 (95.7)	26 (83.9)	
CRT cycle			0.057
1 cycle	9 (19.1)	0 (0)	
2 cycle	38 (80.2)	31 (100.0)	

BMI, body mass index; CRT, chemoradiotherapy; KPS, Karnofsky Performance Score; pCR, pathological complete response.

cancer and *in situ* cervical cancer.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the medical ethics committee of Taizhou Hospital of Zhejiang Province. All included patients provided signed informed consent.

Neoadjuvant chemotherapy

Patients received either the VP1 or VP2 chemotherapy regimen every 3 weeks for two cycles. The VP1 regimen was vinorelbine 25 mg/m^2, intravenous (IV) bolus, days 1 and 8 and cisplatin 75 mg/m^2, IV within 3 hours, day 1. The VP2 regimen was vinorelbine 25 mg/m^2, IV bolus, days 1 and 8 and cisplatin 25 mg/m^2, IV within 2 hours on days 1 to 4.

When the absolute neutrophil count >1.5×10^9/L and the platelet count ≥75×10^9/L, a full-dose of chemotherapy was given. Otherwise, chemotherapy was delayed for up to 2 weeks until the counts recovered. When hematological toxicity persisted for 2 weeks or longer, chemotherapy was discontinued.

Neoadjuvant radiotherapy

A total dose of 40.0 Gy was administered in 20 fractions of 2.0 Gy, five fractions per week, starting on the first day of the first cycle of chemotherapy. All patients were treated with external beam radiation, using the three-dimensional conformal radiation technique. The gross tumor volume was defined by the primary tumor and any enlarged regional lymph nodes. The clinical target volume provided a proximal and distal margin of 3 cm and a radial margin of 0.5 to 1.0 cm radial around the gross tumor volume. The planning target volume provided an 8-mm margin of the clinical target volume.

Surgery

Surgery was performed 4–6 weeks after chemoradiotherapy. Surgery consisted of McKeown or Ivor Lewis esophagectomy, including two-field lymphadenectomy with total mediastinal lymph node dissection. The left and right recurrent laryngeal nerve nodes were mandatorily dissected.

Follow-up

Post-treatment follow-up was performed once every 3 months within the first year, and every 6 months thereafter until death. The primary endpoint was OS, which was measured from the date of group assignment to the date of death or the last follow-up.

Statistical analysis

Normally distributed continuous data were expressed as

Table 2 Overall survival of patients receiving VP1 or VP2 regimen

Regimen	No. (%)	Overall survival range (months)	Median overall survival (95% CI)	Hazard ratio (95% CI)	P value
VP1	47 (60.3)	3.63–103.00	–*	1.000	
VP2	31 (39.7)	4.56–83.90	97.6 (85.6–109.7)	1.008 (0.999–1.018)	0.509

*, the median overall survival was not reached by the date of data cutoff. 95% CI, 95% confidence interval.

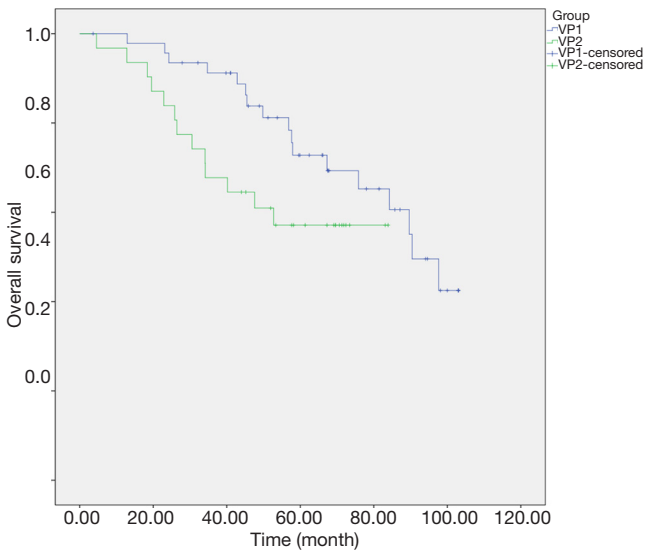

Figure 1 Overall survival curves by group. All values were less than 0.05.

mean ± standard deviation (SD). Frequencies were adopted to describe the categorical variables. The demographic and clinical parameters of patients in the VP1 and VP2 groups were compared using the *t*-test for continuous variables and the χ^2 test for categorical variables. The Kaplan-Meier method was used to compare OS and disease-free survival (DFS) between the two groups. Statistical analyses were performed using SPSS (IBM SPSS Statistics 19.0, SPSS Inc., Chicago, IL, USA). P≤0.05 was considered to be statistically significant.

Results

Clinical characteristics of the study population

A total of 78 patients who had received either the VP1 or VP2 regimen chemotherapy plus radiation followed by surgery were included in the present study. There were 47 patients in the VP1 group and 31 patients in the VP2 group (*Table 1*). The clinical characteristics, including age, gender, tumor location, and clinical stage etc., were not significantly different between the two groups.

Efficacy

The median OS was 97.6 months (85.6–109.7) in the VP2 group, which was not significantly different with that of the VP1 group [hazard ratio (HR), 1.008 (0.999–1.108); P=0.509]. The median OS was not reached by the date of data cutoff (*Table 2*, *Figure 1*). The OS rate in the VP2 and VP1 groups was 86.4% and 94.7% at 1 year, 71.6% and 79.8% at 2 years, and 65.4% and 73.9% at 3 years, respectively (*Table 3*).

Safety profile

The hematologic and non-hematologic toxicity observed during nCRT are listed in *Table 4*. Hematologic toxicity was common, especially leukopenia and neutropenia. Digestive tract adverse reactions mainly included anorexia, vomiting, and radiation esophagitis, but were mostly grade 1 or 2.

The rate of all grades of hematologic adverse events, including anemia, leukopenia, neutropenia, and thrombocytopenia, were significantly higher in the VP2 group compared to the VP1 group (P<0.05). Grade 3 or 4 leukopenia occurred in 27.6% patients in the VP1 group, which was significantly lower than that of the VP2 group (54.8%) (P=0.047). Also, grade 3 or 4 neutropenia was observed in 10.5% patients in the VP1 group, which was significantly lower than that of the VP2 group (35.5%) (P=0.029).

As for non-hematologic toxicity, the rate of all grades of anorexia, vomiting, and fatigue were significantly higher in the VP1 group than those of the VP2 group (all P<0.05). However, there was no difference in the grade 3 or 4 non-hematologic adverse events between the two groups (all P>0.05). No grade 3 or 4 hepatic dysfunction, diarrhea, constipation, or alopecia occurred in either group.

The postoperative complications that occurred in patients of both groups are listed in *Table 5*. Pulmonary infection, arrhythmia, and anastomotic leakage were

common in both groups. Pulmonary infection occurred in four patients (8.5%) in the VP1 group, and eight patients (25.8%) in the VP2 group (P=0.038). However, other postoperative complications, including hemorrhage, pneumothorax, atelectasis etc., were similar between the two groups (all P>0.05).

Discussion

It is important to determine the optimized dose and intensity of neoadjuvant chemotherapy for EC, especially in terms of toxicity. The VP regimen is an effective and promising treatment combination for ESCC, and is worthy of further exploration (17-20). However, its administration pattern varies in different hospitals of China due to the lack of a standard. Therefore, in this study, we compared the safety and efficacy of two commonly applied dose-intensity VP regimens in patients with locally advanced ESCC.

According to the survival analysis of the present study, the median OS was 97.6 months in patients receiving VP2, with a 3-year survival rate of 65.4%; the median OS in VP1 group was not obtained, and the 3-year survival rate was 73.9%. This median OS and 3-year survival rate in the VP2 group were superior to than those reported by Liu *et al.* in 2015, who noted a median OS of 52.8 months and a 3-year OS rate of 64.3% among 57 patients with stage IIb/III ESCC who also received the VP1 regimen (cisplatin 75 mg/m^2 on day 1; vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles) (20). The VP1 regimen was also reported as neoadjuvant chemotherapy for locally advanced ESCC patients by Fu *et al.* (17) and Yang *et al.* (18), but the survival outcomes for patients receiving the VP1 regimen were not reported. Similarly, the VP2 regimen neoadjuvant chemotherapy had been applied for locally ESCC by Zhu *et al.*, however its benefit on survival was not clear (19). This is the first time that the survival outcomes of patients with locally advanced ESCC who received VP2 nCRT followed by surgery have been reported.

In the present study, the median OS was not significantly

Table 3 Overall survival rate of patients receiving VP1 or VP2 regimen

Regimen	1-year OS (95% CI) (%)	2-year OS (95% CI) (%)	3-year OS (95% CI) (%)
VP1	94.7 (87.8–97.8)	79.8 (70.1–86.6)	73.9 (63.5–81.7)
VP2	86.4 (79.0–91.3)	71.6 (62.7–78.7)	65.4 (56.2–73.2)

95% CI, 95% confidence interval.

Table 4 Adverse events of patients receiving VP1 or VP2 regimen

Regimen	VP1 (n=47)			VP2 (n=31)			P for difference in all grades	P for difference in grade 3 or 4
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4		
Anemia	10 (21.3)	1 (2.1)	0	17 (54.8)	0	1 (3.2)	0.021	0.337
Leukopenia	32 (69.1)	8 (17.0)	5 (10.6)	22 (71.0)	12 (38.7)	5 (16.1)	0.010	0.047
Neutropenia	27 (57.4)	3 (6.2)	2 (4.3)	18 (58.1)	7 (22.6)	4 (12.9)	0.019	0.029
Thrombocytopenia	2 (4.3)	1 (2.1)	1 (2.1)	8 (25.8)	2 (6.5)	0	0.020	0.455
Hepatic dysfunction	1 (2.1)	0	0	3 (9.7)	0	0	0.139	–
Anorexia	19 (40.6)	0	0	19 (61.3)	2 (6.5)	0	0.041	0.078
Vomiting	14 (29.8)	2 (4.3)	0	19 (61.3)	2 (6.5)	0	0.029	0.667
Radiation esophagitis	9 (19.1)	2 (4.3)	0	17 (54.8)	1 (3.2)	0	0.006	0.817
Diarrhea	2 (4.3)	0	0	2 (6.5)	0	0	0.452	–
Constipation	4 (8.5)	0	0	3 (9.7)	0	0	0.381	–
Fatigue	2 (4.3)	1 (2.1)	0	5 (16.1)	0	0	0.027	0.414
Fever without infection	6 (12.8)	0	0	1 (3.2)	0	0	0.336	–
Alopecia	1 (2.1)	0	0	1 (3.2)	0	0	0.764	–

Data presented as No. (%). Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

Table 5 Postoperative complications of patients receiving VP1 or VP2 regimen

Postoperative complications	VP1 group (n=47)	VP2 group (n=31)	P value
Hemorrhage	0	0	–
Pulmonary infection	4 (8.5)	8 (25.8)	0.038
Pneumothorax	2 (4.5)	2 (6.5)	0.667
Atelectasis	0	0	–
Respiratory failure	0	0	–
Empyema	0	0	–
Arrhythmia	5 (10.6)	4 (12.9)	0.759
Heart failure	1 (2.1)	1 (3.2)	0.764
Anastomotic leakage	2 (4.3)	3 (9.7)	0.339
Gastric fistula	0	0	–
Chylothorax	1 (2.1)	0	0.603
Pyloric obstruction	0	1 (1.4)	0.414
Intestinal obstruction	1 (2.1)	0	0.414
Injury of recurrent nerve	3 (6.4)	0	0.151
ARDS	0	0	–
Incision infection	2 (4.3)	1 (3.2)	0.817
Fat necrosis of incision	0	1 (3.2)	0.215
ACS	1	0	0.414
Pleural effusion	0	0	–
Anastomotic stenosis	3 (6.4)	0	0.151

Data presented as No. (%). ARDS, acute respiratory distress syndrome; ACS, acute coronary syndrome.

different between the VP1 and VP2 groups (P=0.075). The 1-, 2-, and 3-year OS rates were higher in the VP1 group, although the difference was not statistically significant. This result demonstrated that the VP1 and VP2 regimens were comparable in terms of OS.

Previous studies have demonstrated that the VP1 and VP2 regimens were generally well-tolerated, but may lead to myelosuppression, and were thus associated with increased hematologic toxicity (6,17-20). As reported by Liu *et al.* (20), the incidence of grade 3 or 4 leukopenia and neutropenia related to VP1 were 33.3% and 31.6%, respectively. Conroy *et al.* reported that the rate of grade 3 or 4 neutropenia among advanced ESCC patients was 41% (cisplatin 80 mg/m^2 on day 1; vinorelbine 25 mg/m^2 on days 1 and 8, for two cycles) (6). These results were similar to our findings for the VP1 regimen. Furthermore, compared with VP1, the VP2 group showed significantly higher rates of all grades of anemia, leukopenia, neutropenia, and thrombocytopenia (all P<0.05). Therefore, VP2 exhibited more hematologic toxicity than VP1. Digestive tract adverse events such as anorexia, vomiting, radiation esophagitis etc. were also common, but were mostly grade 1 or 2. As for the frequency of non-hematologic adverse events of grade 3 or 4, the two groups showed no significant differences (all P>0.05). On the whole, VP1 had a better safety profile than VP2, mainly reflected in hematologic toxicity. This result corresponds to the higher compliance rate in the VP1 group, which demonstrated that VP1 confers better tolerance.

Pulmonary infection, arrhythmia, and anastomotic leakage were the most common postoperative complications in our study. This is consistent with the study performed by Liu *et al.* (20) in which pulmonary complications, cardiac complications, and anastomotic leakage were the top three most common surgical complications. Of all the surgical complications, the frequency of pulmonary infection was significantly higher in the VP2 group compared to the VP1 group (25.8% *vs.* 8.5%, P=0.038), while the frequencies of other complication were similar between the two groups (all P>0.05). This result may be associated with the more severe myelosuppression in the VP2 group, as indicated by higher rates of leukopenia and neutropenia.

In summary, VP1 nCRT is comparable with VP2 in terms of survival among locally advanced ESCC patients. However, it has better compliance, tolerance, and safety profile. Therefore, we recommend the use of VP1 over VP2 for neoadjuvant chemotherapy in ESCC.

There are several limitations in our study that should be noted. Firstly, this is a retrospective cohort study, which, in contrast to a prospective randomized control study, exhibits selection bias. However, the clinical characteristics between two groups were not significantly different. Secondly, all of the included patients were diagnosed with an ESCC subtype, and thus the results may not be generalizable to the EC population, including the adenocarcinoma subtype.

Conclusions

The VP1 regimen showed comparable efficacy to the VP2 regimen in terms of survival, but was associated with better compliance, as well as less hematologic toxicity and postoperative pulmonary infection. Therefore, we recommend VP1 over VP2 to be the optimized VP

neoadjuvant chemotherapy regimen for locally advanced ESCC.

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Footnote

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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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University. All included patients provided signed informed consent.

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