Gemcitabine Plus Vinorelbine as Second-Line Therapy in Patients With Metastatic Esophageal Cancer Previously Treated With Platinum-Based Chemotherapy

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We evaluated the efficacy and feasibility of the combination of gemcitabine plus vinorelbine in patients with platinum-based chemotherapy-refractory esophageal cancer. We enrolled 35 patients who received gemcitabine plus vinorelbine as second-line treatment after platinum-based chemotherapy failure between May 2009 and April 2012. Dosage: gemcitabine 1,000 mg/m^2 plus vinorelbine 25 mg/m^2; all drugs were administered on days 1 and 8 of a 21-day cycle, and this was continued until failure or unacceptable toxicity. A total of 125 cycles of treatment were administered, and all patients received at least two cycles of treatment (two to five cycles; median number of cycles: three). Thirty-two patients were evaluable for response. The response rate was 31.3%, and the disease control rate (partial response plus stable disease) was 62.5%. The progression-free survival (PFS) was 4.3 ± 0.2 months [95% confidence interval (CI), 4.0–4.6], and the median overall survival (OS) was 7.3 ± 0.3 months (95% CI, 6.7–7.8). In the subgroup analysis, median PFS was 4.0 ± 0.2 months (95% CI, 3.6–4.3) in patients with high expression of miRNA-214, while it was 4.6 ± 0.3 months (95% CI, 4.1–5.1) in patients with low expression of miRNA-214 (log rank = 0.023). Myelosuppression with neutropenia and thrombocytopenia was the most common side effect observed with this combination regimen, and higher than grade 3 neutropenia and thrombocytopenia were observed in 10 (31.3%) and 8 patients (25.0%), respectively. Grade 3 fatigue was the most common nonhematologic toxicity, which was observed in 2 (6.1%) patients. The combination of gemcitabine plus vinorelbine was well tolerated as second-line treatment for platinum-based chemotherapy-refractory esophageal cancer patients and appeared to provide enhanced clinical activity especially in patients with low expression of miRNA-214.

Key words: Advanced esophageal cancer; Second-line treatment; Gemcitabine plus vinorelbine; Platinum-based chemotherapy; miRNA-214; Progression-free survival

INTRODUCTION

Esophageal cancer is a highly aggressive neoplasm with a strong tendency for invasion and metastasis, and despite the use of multimodality therapy, it remains one of the leading causes of cancer-related deaths in the world. Unfortunately, esophageal cancer rarely presents at an early stage, and patients are usually not diagnosed until the cancer has reached an advanced stage, at which point surgical resection with radical esophagectomy is not feasible. Therefore, chemotherapy plays an important role in patients with metastatic disease. The combination of cisplatin and 5-fluorouracil (5-FU) is considered the first-line standard regimen. This regimen has demonstrated an overall response rate of 25% to 45%, with a median survival of less than 1 year. Unfortunately, patients experience recurrence or disease progression with standard chemotherapy. Therefore, it is important to establish second-line chemotherapy regimens after failure of the standard cisplatin and 5-FU chemotherapy.

Vinorelbine is a synthetic vinca alkaloid, and it has a favorable toxicity profile and activity against a wide range of human malignancies, including non-small cell lung cancer, breast cancer, ovarian cancer, and esophageal squamous cell carcinoma (ESCC). In a clinical trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC), this drug was administered on a weekly basis at a dose of 25 mg/m^2: 6 of 30 previously untreated patients (20%) and 1 of 16 previously

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treated patients (6%) had a major response7. Gemcitabine is a deoxycytidine analog, and it has also been tested in esophageal cancer, with significant clinical activity and manageable toxicity in patients with advanced esophageal cancer8,9. A phase II trial of gemcitabine and cisplatin in patients with recurrent or metastatic ESCC had shown an overall response rate of 42.1%. Median progression-free survival (PFS) and median survival for all patients were 4.1 and 10 months, respectively. Patients with a response had significantly longer median survival compared with patients without a response (11 months vs. 7.5 months, \( p = 0.0069 \)). Overall survival (OS) at 1 year was 36.8%, at 2 years it was 10.5%, and at 5 years it was 5.3%. The most common grades 3–4 toxicity for all patients was leucopenia (44.7%)10. One clinical study of single-agent vinorelbine for pretreated or metastatic squamous cell carcinoma of the esophagus had shown that partial responses were observed in 4 of 14 symptomatic patients. In general, toxicity was mild, with only one episode each of grade 4 neutropenia and constipation, respectively11.

MicroRNAs (miRNAs) are a group of small noncoding RNAs that regulate gene expression at the posttranscriptional level. There is evidence showing that differential expression of miRNAs was correlated with survival in patients with esophageal carcinoma12,13. miRNA expression profiles may become useful biomarkers for cancer diagnostics, prognosis, and prediction of response to treatment14. Recent evidence demonstrates that miRNAs may function similarly to oncogenes or tumor suppressors, suggesting that they may play an important role in tumorigenesis15. Zhang et al. confirmed that pri-miR-124-1 rs531564 and pri-miR-34 rs4938723 were associated with an increased risk of ESCC in Chinese patients16. Another study has shown that miR-335 expression is an independent prognostic factor for patients with esophageal cancer, thereby identifying it as a potential valuable biomarker for ESCC17.

MATERIALS AND METHODS

Patients

A total of 35 patients were enrolled between May 2009 and April 2012 at the Shandong Tumor Hospital in Jinan, China. The diagnosis of metastatic esophageal cancer was confirmed by histology and cytology prior to patients being treated with gemcitabine plus vinorelbine as second-line treatment after platinum-based chemotherapy failure. The patient selection criteria for this study were as follows: age 18–75 years; an Eastern Cooperative Oncology Group performance status of 0–2; life expectancy of ≥3 months and with one measurable lesion at least according to the modified response evaluation criteria in solid tumors (RECIST); adequate bone marrow function (white blood cell count ≥4.0 × 10⁹/L, absolute neutrophil count ≥1.5 × 10⁹/L, and platelet count ≥100 × 10⁹/L); adequate renal function (serum creatinine level ≤1.5 mg/dl); adequate liver function [total bilirubin level ≤1.5 mg/dl, and aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase levels ≤2.5 × the upper limit of normal]. Patients were excluded from this trial with one of the following criteria: massive pleural effusion or ascites, active concomitant second malignancy, brain metastasis, prior systemic treatment with either gemcitabine or vinorelbine, pregnancy, or women who were breastfeeding. All patients had to give informed consent and to agree to be treated with this combination chemotherapy regimen. The clinical trial was authorized by the ethics committee of Shandong Tumor Hospital.

Treatment

The treatment schedule was as follows: gemcitabine was administered at a dose of 1,000 mg/m² over 30 min and then followed by vinorelbine at a dose of 25 mg/m² as a slow (10 min) intravenous bolus. Both drugs were administered on days 1 and 8 of a 21-day cycle. Each treatment cycle was repeated until the appearance of disease progression, unacceptable toxicity, or up to a total of six cycles. Prior to treatment, peripheral blood was collected in all patients for determination of serum miRNA levels.

| Table 1. Patient Characteristics (N=35) |
|----------------------------------------|
| Factor                  | Patients (%) |
| Age (median, 65.5; range, 39–74)     | |
| <65 years                | 15 (42.9)    |
| ≥65 years                | 20 (57.1)    |
| Gender                   |              |
| Male                     | 30 (85.7)    |
| Female                   | 5 (14.3)     |
| Performance status       |              |
| 0                        | 9 (25.7)     |
| 1                        | 15 (42.9)    |
| 2                        | 11 (31.4)    |
| Histology                |              |
| Squamous cell carcinoma  | 34 (97.1)    |
| Adenocarcinoma           | 1 (2.9)      |
| Prior treatment          |              |
| Concurrent chemoradiotherapy | 16 (45.7)   |
| Chemotherapy plus radiotherapy | 12 (34.3)  |
| Chemotherapy             | 7 (20.0)     |
| Sites of metastasis      |              |
| Distant lymph notes      | 20 (57.1)    |
| Lung                     | 9 (25.7)     |
| Liver                    | 4 (11.4)     |
| Both                     | 2 (5.7)      |
Evaluation and Statistical Analysis

Tumor response was initially assessed after the second chemotherapy cycle by computed tomography (CT) scan using RECIST criteria and every two cycles thereafter. On the basis of the RECIST guideline, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined. PFS was determined from the date of treatment initiation to documentation of disease progression or death. OS was determined from the time of treatment initiation with gemcitabine combined with vinorelbine until death or the last follow-up. The Kaplan–Meier method was utilized to construct the PFS and OS curves.

RESULTS

Patient Characteristics

A total of 35 patients were enrolled in this study between May 2009 and April 2012. Thirty-four of 35 patients had squamous cell carcinoma, with only 1 patient having adenocarcinoma. All patients had previously received platinum-based chemotherapy. In those patients who had been previously treated, 16 (45.7%) patients had undergone

![Figure 1. PFS in population.](image-url)
concurrent chemoradiotherapy, and 12 (34.3%) patients had received chemotherapy and radiotherapy, albeit not concurrently, including systemic chemotherapy alone in 7 patients. All patients had metastatic disease; 20 patients presented with metastases to a distant lymph node, 9 with lung metastases, and 4 with liver metastases. Sites of metastasis were confirmed by histology/cytology. The patient characteristics are presented in Table 1.

**Clinical Activity**

A total of 125 cycles of treatment were administered, and all patients received at least 2 cycles of therapy (2–5 cycles; median, 3). Thirty-two patients were evaluable for response. Of this group, 10 patients (31.3%) had a PR, 10 patients (31.3%) had an SD, and 12 patients (37.5%) had a PD. No CR was observed in this trial (Table 2). The overall response rate was 31.3%, and disease control rate (PR plus SD) was 62.5%. Median PFS was 4.3 ± 0.2 months [95% confidence interval (CI), 4.0–4.6] (Fig. 1), and the median OS was 7.3 ± 0.3 months (95% CI, 6.7–7.8) (Fig. 2). In the subgroup analysis, the PFS was significantly different in patients with high expression of miRNA-214 when compared to low expression. The PFS was 4.0 ± 0.2 months (95% CI, 3.6–4.3) and 4.6 ± 0.3 months (95% CI, 4.1–5.1) in high and low expression of miRNA-214, respectively (log rank = 0.023) (Fig. 3).

In general, the safety profile of the combination regimen was manageable, and no treatment-related deaths were observed. At the time of final analysis, all patients had discontinued treatment. Hematologic toxicity was the most important side effect, including neutropenia and thrombocytopenia. Grade 3/4 neutropenia and thrombocytopenia were observed in 10 (31.3%) and 8 (25.0%) patients, respectively. Nonhematologic side effects included diarrhea, nausea/vomiting, neurotoxicity, fatigue, alopecia, and constipation. Grade 3 fatigue was observed in two patients (6.1%). However, no grade 4 nonhematologic toxicity was observed in this study (Table 3).

**DISCUSSION**

The overall prognosis for patients with metastatic or recurrent esophageal cancer is extremely poor, with median survival in the range of 4–8 months\(^18,19\). Several different chemotherapy regimens have been associated with encouraging clinical activity as first-line chemotherapy for metastatic or recurrent esophageal cancer, but the median duration of response is generally short\(^20,21\). As such, there remains an urgent need to identify effective and well-tolerated second-line treatment regimens.

The vinca alkaloid vindesine has shown a 17% response rate in pretreated small cell esophageal carcinoma (SCEC) patients; however, this agent was associated with significant toxicity, with half of the patients experiencing peripheral neuropathy and one treatment-related death. In contrast, vinorelbine has shown a similar response rate, albeit with reduced toxicity\(^7,23\). In a study of previously treated metastatic squamous cell carcinoma of the esophagus, single-agent vinorelbine had a 25% response rate. Only one patient experienced grade 4

![Figure 2. OS calculated from the date of treatment with gemcitabine plus vinorelbine.](image-url)
neutropenia and constipation. A phase II study of vinorelbine plus cisplatin in previously untreated patients with metastatic squamous cell esophageal carcinoma showed a 33.8% response rate. This combination was associated with a median PFS of 3.6 months and a median OS of 6.8 months. Toxicity was mainly related to neutropenia. The combination of docetaxel and vinorelbine in recurrent squamous cell esophageal carcinoma resulted in an overall response rate of 60%, which included 3 of 20 CRs (15%) and 9 of 20 PRs (45%). Median response duration was 7 months, and median OS was 10.5 months. Neutropenia was the most frequent and severe toxicity (grade 4 in 80%; grade 3 in 20%).

Single-agent irinotecan or the combination of irinotecan plus docetaxel in cisplatin-pretreated metastatic esophageal cancer was associated with a median PFS of 2 months and a median OS time of 4.5 months. The response rate was relatively low at 12.5% (95% CI 2.7–32.4%). The incidence of grade 3 hematologic toxicity was rare. Several clinical studies have investigated docetaxel plus cisplatin or single-agent paclitaxel for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy, and the overall response rates have been in the 10.3–44.2% range, median PFS of 2.1–4.8 months, and OS of 7.2–10.4 months. The main grade 3/4 hematologic toxicities have been myelosuppression in the form of neutropenia (48.8–52.8%) and leucopenia (45.3–47.3%), respectively.

An earlier study showed that miRNA expression correlated with response to therapy and overall prognosis in esophageal cancer. Figures and tables were included to illustrate the data.
acute myelogenous leukemia. Two studies have demonstrated aberrant expression of miRNAs in ESCC and that these miRNAs were involved in several biological processes by targeting different miRNAs. In one study, the miRNA expression level was compared in matched ESCC tissues and normal tissues by quantitative polymerase chain reaction, and it was determined that expression levels of miR-98, miR-101, and miR-214 were significantly lower in tumor than in normal tissues. A different study showed that overexpression of miR-214 decreased the sensitivity of the cells to gemcitabine and that miR-214 could induce cell survival and cisplatin resistance through targeting the phosphatase and tensin homolog (PTEN) pathway.

In conclusion, the combination of gemcitabine plus vinorelbine was well tolerated in the second-line treatment of platinum-based chemotherapy-refractory esophageal cancer patients. Moreover, this combination appears to have improved clinical activity, at least in terms of PFS, in patients whose tumors express reduced levels of miRNA-214. One of the potential limitations of this study is the relatively small patient size. However, based on the promising clinical activity and manageable safety profile observed in this clinical study, the combination of gemcitabine plus vinorelbine merits further clinical investigation.

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