Incidence of Injection Site Reactions Induced by Vinorelbine and Prevention with Hot Compresses

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Abstract
Objective: Patients treated with vinorelbine (VNR)-containing chemotherapy often suffer from injection site reactions. VNR is a moderate vesicant that is well known to cause local venous damage. We conducted this study to identify clinical risk factors related to the incidence of injection site reactions caused by VNR, and whether applying a hot compress was effective for preventing such reactions.

Methods: Medical records were retrospectively investigated for 48 patients treated with chemotherapy regimens containing VNR. Injection site reactions were evaluated for every course and were graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0). Gender, age, body mass index, chemotherapy regimen, dose of VNR, and volume of fluid for flushing the vein were assessed as clinical variables. A hot compress was applied to the vein proximal to the injection site during VNR injection.

Results: The injection site reactions occurred in 29 (60%) among 48 patients received intravenous VNR injection. According to multivariate analysis, use of gemcitabine (GEM) in combination with VNR showed a significant independent correlation with an increased risk of injection site reactions \( p < 0.019 \). When hot compress was applied to 21 patients, who experienced phlebitis of VNR, the injection site reaction was occurred to only three patients \( p < 0.001 \).

Conclusion: In this study, the risk factor of the injection site reaction by VNR seems to be combination of GEM. Application of hot compresses was effective for preventing injection site reactions by VNR.

Key words: vinorelbine, injection site reaction, hot compress, risk factor

Introduction

Patients often suffer from local venous problems, including pain, itching, swelling, and erythema, when treated with vinorelbine (VNR)-containing chemotherapy. VNR is currently one of the most active agents for a variety of solid tumors and it is often used for the treatment of metastatic non-small-cell lung cancer (NSCLC)1,2, breast cancer3, and Hodgkin’s disease4. In clinical studies, the toxicities frequently reported for VNR have included myelosuppression, constipation, and peripheral neuropathy, with all of these being mild to moderate5, 11. VNR is also a moderate vesicant that is known to cause venous irritation and an incidence of 10-50% has been reported in patients who received peripheral infusion of this drug6, 7-10. Venous irritation generally includes injection site reactions, local reactions, and superficial phlebitis. Symptoms include erythema, pain at the injection site, and discoloration and tenderness along the vein7. Several investigators have tried to reduce the incidence of injection site reactions by various methods11-13. However, the exact mechanisms responsible for these reactions remain unknown and the risk factors related to injection site reactions following the peripheral infusion of VNR have never been reported. Yokota et al. reported the combination of hot compresses and increase of physiological saline for washing out was an effective treatment to prevent phlebitis caused by VNR14. But it is not clear in whether the care of hot compresses is effective for preventing injection site reaction.

We conducted the present study to identify clinical risk factors related to the occurrence of injection site reactions after peripheral infusion of VNR, and whether application of hot compresses was effective for preventing these adverse reactions.

Subject and Methods

1. Patients

We retrospectively reviewed the medical records of 48 patients treated with a chemotherapy regimen containing vinorelbine between April 2009 and July 2010 at the
National Hospital Organization Kanazawa Medical Center. The chemotherapy regimens consisted of vinorelbine at 20-25 mg/m² weekly, either alone or in combination with cisplatin, carboplatin, gemcitabine, mitomycin-C, or trastuzumab. In all combination chemotherapy regimens, VNR was selected ahead of other drugs. We extracted patients in whom VNR was infused via peripheral veins. VNR was diluted in 50 ml of normal saline and was infused into a peripheral vein over a period of 5 to 10 min. All patients who received at least one dose of VNR were eligible for this study. The clinical characteristics of the patients are listed in Table 1.

2. Evaluation of Injection Site Reactions
Data from the medical records were used to evaluate injection site reactions after every course of chemotherapy and each reaction was graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0) for injection site reactions (grade 0: none; grade 1: pain, itching or erythema; grade 2: pain or swelling with inflammation or phlebitis; and grade 3: ulceration or necrosis that is severe or prolonged or requires surgery). Injection site reactions were also categorized as present or absent, with present being defined as occurrence of a grade 1 or worse reaction at least once during treatment.

3. Prevention of Injection Site Reactions with Hot Compresses
We studied the prevention of injection site reactions in 21 patients who had previously developed symptoms after receiving VNR. In these patients, the vein proximal to the injection site was warmed by application of a hot compress during VNR injection.

4. Statistical Analysis
The correlation between the incidence of injection site reactions and each of the clinical variables was evaluated by Fisher’s exact test, as appropriate. We used gender, age, BMI, chemotherapy regimen, dose of VNR, and volume of fluid for flushing the vein as clinical variables. Multivariate analysis was performed by the logistic regression procedure to determine the relationship between the incidence of injection site reactions and each of these variables. A two-sided statistical test was used in all analyses and p values <0.05 were considered to be significant. Preventive effect of hot compress were tested using Fisher’s exact test as appropriate. Statistical analysis software (Dr SPSS for windows, Version 3.0) was used for these analyses.

This study was approved by the research ethics committee of Kanazawa Medical Center (No2011-050).

Results
1. Incidence of Injection Site Reactions
Injection site reaction occurred in 29 of the 48 patients (60%), and during 48 of 331 infusions (15%). The onset of the injection site reactions was seen early after the VNR infusion, with 65% of the events occurring on the day after the infusion Fig. 1. The time to disappearance of symptoms was one day in 54% (n=26). Grade 1 injection site reactions was observed in 69% (n=33), grade 2 in 13% (n=6), and grade 3 in 19% (n=9).

2. Multivariate Analysis
The results of multivariate analysis of the six variables investigated (gender, age, BMI, chemotherapy regimen, dose of VNR, and flushing volume) are shown in Table 2. Combination chemotherapy with GEM was shown to be a significant independent variable correlated with an increased risk of injection site reactions (p=0.019).
3. Prevention of Injection Site Reactions with Hot Compresses

When hot compresses were applied to 21 patients, who had previously developed some injection site reactions by VNR, it was effective for preventing the injection site reactions in 18 patients (Table 3), and the number of events was significantly decreased ($p<0.001$). Three cases of injection site reactions which occurred prevention with hot compresses were all grade 1.

Discussion

The combination of VNR and GEM was associated with a significantly higher risk of injection site reactions compared with other VNR-containing regimens ($p<0.001$).

In patients receiving parenteral nutrition, it has been reported that the pH and osmolality of the solution influence the occurrence of phlebitis[7]. With regard to GEM, it has been reported that pH and osmotic pressure have an influence[8]. The osmolality ratio to saline is 0.1 for VNR, 2 for GEM, 0.8–1.2 for CDDP, 1 for MMC, 1 for CB-DCA, and 1 for HER[9–24]. Thus, the osmolality of VNR and GEM is further from the physiological range compared with other drugs. Moreover, the pH of the drug solution is 3.3–3.8 for VNR, 3 for GEM, 2–5.5 for CDDP, 5.5–8.5 for MMC, 5–7.0 for CB-DCA, and 5.8–6.4 for HER[19–24]. Therefore, the occurrence of phlebitis after infusion of VNR, GEM, and CDDP might be ascribed to the pH of these drug solutions. A previous study indicated that slow infusion prevents phlebitis due to pH[25]. However, slow infusion of GEM aggravates hematologic toxicity[25], so the recommended time is 30 min and we administered GEM over 30 min for all patients. VNR is also a moderate vesicant, and slow infusion of VNR leads to cell necrosis, while rapid injection prevents phlebitis due to VNR[11–13]. On the other hand, the infusion time of CDDP was two hours and there was little influence on injection site reactions. Therefore, we consider that the combination of VNR and GEM was the main risk factor for injection site reactions. There are some limitations to the present study. According to univariate analysis, there was no significant difference in the incidence of injection site reactions.

![Onset of injection site reaction for 48 cases](image.png)

**Fig. 1** Onset of injection site reaction for 48 cases

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Multivariate analysis about relationship between clinical variables and injection site reaction</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Gender (male, female)</td>
<td>0.53</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.996</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.84</td>
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<tr>
<td>VNR dose (mg/body)</td>
<td>1.02</td>
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<tr>
<td>Chemotherapeutic regimen (VNR+GEM, others)</td>
<td>6.93</td>
</tr>
<tr>
<td>Volume of flushing vein (mL) (≥100, &gt;100)</td>
<td>1.69</td>
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VNR, vinorelbine; GEM, gemcitabine.

<table>
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<tr>
<th>Table 3</th>
<th>Prevention effect of injection site reaction with hot compresses</th>
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<tr>
<td>Timing of injection</td>
<td>No. of patients</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Before prevention with hot compresses</td>
<td>48</td>
</tr>
<tr>
<td>After prevention with hot compresses</td>
<td>21</td>
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—10(10)—
between VNR alone (56%) and GEM + VNR (79%). However, there was a significant difference on multivariate analysis. We thought possibility that concomitant agents other than GEM may have suppressed the induction of injection site reactions by VNR, but our research could not clarify the reason due to the small number of cases.

There was a report that patients with a high BMI are prone to develop venous irritation and phlebitis\(^{23}\). However, in this study, there was no relationship between the BMI and the injection site reactions. The reasons for this are considered to include the relationship between obesity and venous thrombosis. Obesity (indicated by a high BMI) is clearly associated with cardiovascular disease and diabetes, and is also a risk factor for venous thrombosis including superficial vein thrombosis and phlebitis\(^{27}\). In our study, cardiovascular disease and diabetes were present in 6.9% (2/29) of the injection site reaction group versus 15.8% (3/19) of the group without injection site reactions and the difference was not statistically significant \(p = 0.32\). We could not clarify the relationship between BMI and injection site reactions induced by VNR. Because an average BMI in this research patients was 21.2 ± 3.1 (kg/m\(^2\)), this is approximation standard of BMI (22 kg/m\(^2\)), and also there is almost no variation, and this was retrospective study.

In 21 patients who had a history of injection site reactions were cared for hot compress. Application of hot compresses significantly reduced injection site reactions \(p < 0.01\), and this method was shown to be useful for prevention of injection site reactions caused by VNR. VNR induces oxidative stress by depleting intracellular glutathione and increasing reactive oxygen species production in porcine aorta endothelial cells, and oxidative stress plays an important role in the VNR-induced cell injury\(^{28}\). Hot compress may dilate the injection site vascular vein and VNR flow early. We considered that because the exposure time of VNR was shortened, cell injury was reduced. This is not contradictory to the report which venous inflammation reduced by bringing intravenous drip speed forward\(^{29}\).

In conclusion, we investigated clinical risk factors related to the incidence of injection site reactions caused by peripheral infusion of VNR. Our findings indicated that use of GEM in combination chemotherapy was associated with a significantly increased risk of venous irritation due to VNR, while the application of hot compresses was an effective method of preventing injection site reactions.

References


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