Incidence of Vascular Pain Following Gemcitabine Chemotherapy Infusion with Modified Diluent

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ABSTRACT

Objective: The objective of this study was to determine incidence and severity of vascular pain following modified dilulent for gemcitabine solution. Gemcitabine (1,000-1,250 mg/m^2) was diluted in 250 ml of normal saline for cancer patients.

Methods: The observational study design was conducted in cancer care unit at our University based hospital. Cancer patients who were treated with gemcitabine based regimen during June to November 2015 were enrolled in the study. Gemcitabine was diluted in 250 ml of normal saline and infused over 30 minutes peripherally. Vascular pain incidence and severity were assessed during and at the end of drug administration by using standard pain assessment tools including pain numeric rating scale, or visual analogue scale (VAS). Incidences of vascular pain were collected and analyzed by descriptive statistics.

Results: One hundred cancer patients receiving pre-specified gemcitabine based regimen were enrolled in the study. The vascular pain incidence was reported in 36 of patients (36%). Among patients with vascular pain, 28 patients (78%) and 8 patients (22%) reported mild and moderate pain severity, respectively. Severe pain was not found in this study. Mean vascular pain score was 1.3±0.56.

Conclusion: This study demonstrated that using 250 ml of normal saline as diluent for gemcitabine chemotherapy, the vascular pain incidence was 36% and the pain score appeared to be minimal. Mean±SD of pain score was 1.3±0.56 and there was no incidence of severe pain.

Keywords: Gemcitabine; vascular pain; normal saline solution (Siriraj Med J 2017;69: 181-184)

INTRODUCTION

Gemcitabine, a deoxycytidine analogue, is classified as antimetabolite antineoplastic drug. Gemcitabine is a prodrug and needs to be metabolized by nucleoside kinase enzyme to di-phosphatenucleoside (dFdCDP). The active form of this drug can inhibit cellular DNA synthesis.

A commercially available form of gemcitabine is lyophilized powder for injection. Following proper dilution, it can be infused peripherally through vein. Gemcitabine has been indicated as single agent or in combination for treatment of many types of cancer including pancreatic cancer, metastatic breast cancer, locally-advanced or metastatic non-small cell lung cancer, bladder cancer, and advanced or relapsed ovarian cancer. Recommended dose of gemcitabine varies from 1,000 - 1,250 mg/m^2 depending on disease stages and cancer type.

According to manufacturer recommendation, gemcitabine lyophilized powder should be reconstituted with 0.9% sodium chloride for injection to make a concentrated solution not greater than 40 mg/ml. Further dilution is with 50 - 500 ml of 0.9% sodium chloride.[1]

Common side effects of gemcitabine includes myelosuppression, peripheral edema, pain, flu-like symptoms, fever, fatigue, nausea, vomiting, skin rash, elevated liver enzymes, hematuria proteinuria and vascular toxicity. Moreover, vascular pain is also the most common adverse reaction which is the important obstacle during drug administration. In our previous practice, 100 ml of 0.9% sodium chloride for injection was

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used for gemcitabine dilution and given over 30-minutes infusion peripherally. Prolongation of infusion time should be avoided as it has been reported to increase toxicity especially myelotoxicity. Severe vascular pain was reported in a quarter of our patients who needed to withhold gemcitabine administration until pain had receded.

The mechanism of vascular pain is still unclear and may be associated with administration technique or another factor.[11] Some clinical studies have suggested co-administration of 5% glucose solution in addition to gemcitabine mixed in 100 ml of normal saline can alleviate vascular pain due to lower concentration.[3] Another clinical study has shown improved vascular pain after changing diluent from normal saline to 5% glucose solution.[2] However, study of further dilution of gemcitabine in normal saline is limited. The objective of this study was to evaluate pain incidence and severity after using modified diluent for gemcitabine solution.

MATERIALS AND METHODS

This was an observational, cross-sectional study which was conducted in out-patient oncology unit at Siriraj Hospital to determine pain incidence and severity in cancer patients after using modified diluents for gemcitabine solution had been introduced. The study was endorsed by the Institution Review Boards Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. (Si.229/2015)

Eligible patients were aged >18 years; had been diagnosed with cancer; had been evaluated by medical oncologist to receive gemcitabine in normal saline 250 ml via peripheral intravenous infusion over 30 minutes, Eastern Cooperative Oncology Group performance status of 0-2; with normal vital signs and body temperature were normal. Patients who had cardiovascular problem, fluid overload problem and/or received gemcitabine via central intravenous line were excluded.

Gemcitabine was diluted in 250 ml of normal saline and infused over 30 minutes peripherally. Pain assessment tools including numeric rating scale, or visual analogue scale (VAS) were used to assess vascular pain during and at the end of gemcitabine administration.[5] Vascular pain incidence was a primary endpoint in this study. The pain intensity score and severity were secondary endpoints.

The sample size was calculated to estimate the expected severe vascular pain around 15% (proportion = 0.15) of patients receiving gemcitabine in normal saline 250 ml with the 95% confidence interval of 7%, so the sample size of 100 patients were planned. Descriptive statistical analysis was applied to report the results. Vascular pain incidence was reported as frequency and percentage. Pain intensity was reported as pain score from 0 to 10. (pain score: 0 = no pain, 1-3=mild pain, 4-6 =moderate pain, 7-10=severe pain).

RESULTS

Between June and November 2015, One hundred patients were enrolled in the study of which 51% were male and 49% were female. Their mean (SD) age was 61±12 years. Non-Small Cell Lung Cancer was the most common cancer followed by pancreatic cancer and cholangiocarcinoama Table 1.

TABLE 1. Patient characteristics (N=100).

Patient characteristic		Value
Age (year)	Mean±SD	61±12
Gender	Male	51 (51.0%)
	Female	49 (49.0%)
Type of cancer	NSCLC	55 (55.0%)
	Pancreatic cancer	11 (11.0%)
	Cholangiocarcinoma	8 (8.0%)
	Bladder cancer	6 (6.0%)
	Breast cancer	5 (5.0%)
	Nasopharynx cancer	2 (2.0%)
	Urothelial cancer of ureter	2 (2.0%)
	Others	11 (11.0%)

The incidence of vascular pain from modified diluent for gemcitabine solution was reported in 36 patients (36%). Among patients who had vascular pain, mean vascular pain score was 1.3±0.56. Pain severity of 28 patients (78%) and 8 (22%) were classified as mild and moderate pain, respectively. Severe vascular pain was not found Table 2.

TABLE 2. Number of patients experienced vascular pain according to pain score and severity.

Pain score	Severity	Patients (%)
0	-	64 (64%)
1 - 3	Mild pain	28 (28%)
4 - 6	Moderate pain	8 (8%)
7 - 10	Severe pain	0 (0%)

DISCUSSION

This study demonstrated the incidence of vascular pain was 36% after using gemcitabine diluted in 250 ml of normal saline. Pain severity ranged from mild to moderate pain. The mean pain score was classified as mild pain (1.3 ± 0.56).

A previous study reported that frequency of vascular pain and pain score were significantly lower when 100 ml of 5% glucose solution had been used as diluent for gemcitabine compared with 100 ml of normal saline, 40% vs 63% and 1.3 vs 2.7, respectively.[2] For the reason of manufacturer recommendation we used normal saline as diluent for gemcitabine. This study introduced another method to reduce vascular pain by modifying diluent for gemcitabine preparation. The incidence of pain and pain severity from gemcitabine diluted in 250 ml normal saline in this study was lower than the previous study, (36% vs 63%). Moreover, pain severity from modified diluent for gemcitabine solution in this study was comparable to gemcitabine diluted in 5% glucose solution in the previous study. However, to apply this comparative result the user needs to be aware before summarized cause from the reason that many confounding factors need to be controlled for comparing results from different clinical studies.

Although the incidence of vascular pain is 36% in this study, pain severity was lower than the use of 100 ml of normal saline as diluent in previous practice. The modified diluent for gemcitabine solution can improve vascular pain intensity. This result may help practitioners to select appropriate volume of diluent for gemcitabine admixture to prevent severe vascular pain. Further study may be required to compare vascular pain incidence and severity between different gemcitabine diluents and concentration to explore the most appropriate conditions for gemcitabine administration.

CONCLUSION

This study demonstrated that when using 250 ml of normal saline instead of 100 ml as diluent for gemcitabine chemotherapy, the vascular pain incidence was 36% with minimal pain score. Mean±SD of pain score was 1.3±0.56 and there was no incidence of severe pain.

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