British Journal of Medicine & Medical Research
2(2): 132-141, 2012

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Dexamethasone as a Means Not Only for Controlling Vascular Pain Caused by the Administration of Oxaliplatin Via the Peripheral Vein But Also for Controlling Oxaliplatin-Induced Hypersensitivity Reactions

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Research Article

Received 5th October 2011
Accepted 23rd December 2011
Online Ready 31st January 2012

ABSTRACT

Background and Aims: With the recent development of capecitabine and oxaliplatin (XELOX) therapy, implantation of a Central Venous (CV) port can be now avoided. However, vascular pain occasionally requires switching of the drip infusion route. Some investigators reported that addition of steroids to oxaliplatin drip infusion is useful in controlling vascular pain. However, the pharmacological use of steroids can make oxaliplatin unstable due to the elevation of pH; further, the effectiveness of steroid in this therapy is unknown. This study was undertaken to evaluate the effectiveness of dexamethasone (DEX) for controlling vascular pain caused by the administration *of* oxaliplatin via the peripheral vein.
Study design: Retrospective study.
Place and duration of the Study: Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, between April 2010 and November 2011.
Methodology: The study included 69 patients who received XELOX + bevacizumab therapy for advanced or recurrent colorectal cancer. In all the patients, oxaliplatin (130 mg/m^2) was administered in combination with DEX (6.6 mg) via the peripheral vein.
Results: Vascular pain developed in 47 patients (68.1%), but it was transient. No patients required CV port implantation. Grade 3 or higher hemotoxicity was noted in 14.5% of the patients, and grade 3 or higher nonhematological toxicity was noted in 20.3% of the

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patients. The response rate was 59.4%. One patient experienced hypersensitivity reactions to oxaliplatin.
Conclusions: The recorded response rate combined with the use of DEX suggests that DEX probably does not exert adverse effects on the therapy, ie, it does not affect the stability of oxaliplatin by elevating the pH. DEX may be useful not only for controlling vascular pain caused by the administration of oxaliplatin via the peripheral vein but also for controlling oxaliplatin-induced hypersensitivity reactions.

Keywords: Oxaliplatin; dexamethasone; vascular pain; hypersensitivity; colorectal cancer.

1. INTRODUCTION

Oxaliplatin, a platinum-based chemotherapeutic agent, has showed marked efficacy for the treatment of advanced colorectal cancer (De Gramont et al., 2000; Tournigand et al., 2004) and in the adjuvant setting (Andre et al., 2004; Petrioli et al., 2008). Unlike other platinum derivatives, oxaliplatin does not result in significant renal impairment or ototoxicity. The dose-limiting toxicity of oxaliplatin is related to the peripheral nerve function and ultimately the development of peripheral neuropathy (Kiernan et al., 2006).

Chemotherapy for colorectal cancer has advanced remarkably with the introduction of folininc acid, fluorouracil, and irinotecan (FOLFIRI); and folinic acid, fluorouracil, and oxaliplatin (FOLFOX); therapies, which require a CV port. Chemotherapy with these regimens is occasionally interrupted by complications associated with the CV port, such as infection, thrombosis, and pinch-off syndrome (Behlendorf et al., 2008). With the recent development of XELOX therapy involving oral administration of drug preparations, etc., implantation of a CV port can be now avoided. However, vascular pain (pain in the peripheral veins) due to phlebitis occasionally requires switching of the drip infusion route during XELOX therapy.

Phlebitis induced by intravenous infusion of antineoplastic agents reduces the completion or continuation of chemotherapy. The causative factors of phlebitis include the pH and osmotic pressure of the solution, size of the vein used, size and material of the catheter, and infusion periods (Kuwahara et al., 1998). A number of methods for avoiding phlebitis have been reported (Nakayama et al., 2002; Curran et al., 1990); however, none of them are completely effective. Thus, there is an urgent need to develop new methods to prevent and alleviate phlebitis. Some investigators reported that addition of steroids to oxaliplatin drip infusion is useful in controlling vascular pain (Matsuyama et al., 2011). However, the pharmacological use of steroids can make oxaliplatin unstable due to the elevation of pH (Jerremalm et al., 2002); further, the effectiveness of oxaliplatin in this therapy is unknown because of lack of published data in this regard. The present study was undertaken to evaluate the effectiveness of DEX for controlling vascular pain caused by the administration of oxaliplatin via the peripheral vein during XELOX therapy.

2. MATERIALS AND METHODS

2.1 Patients

We retrospectively reviewed the medical records of patients diagnosed with colorectal cancer. The selection criteria for inclusion in this analysis were: histologically proven metastatic and unresectable colorectal adenocarcinoma; no prior chemotherapy or receiving adjuvant chemotherapy completed at least 6 months before. Patients who had an active extra colonic malignancy or those who had received prior radiotherapy were also excluded. Informed consent was obtained from all patients.

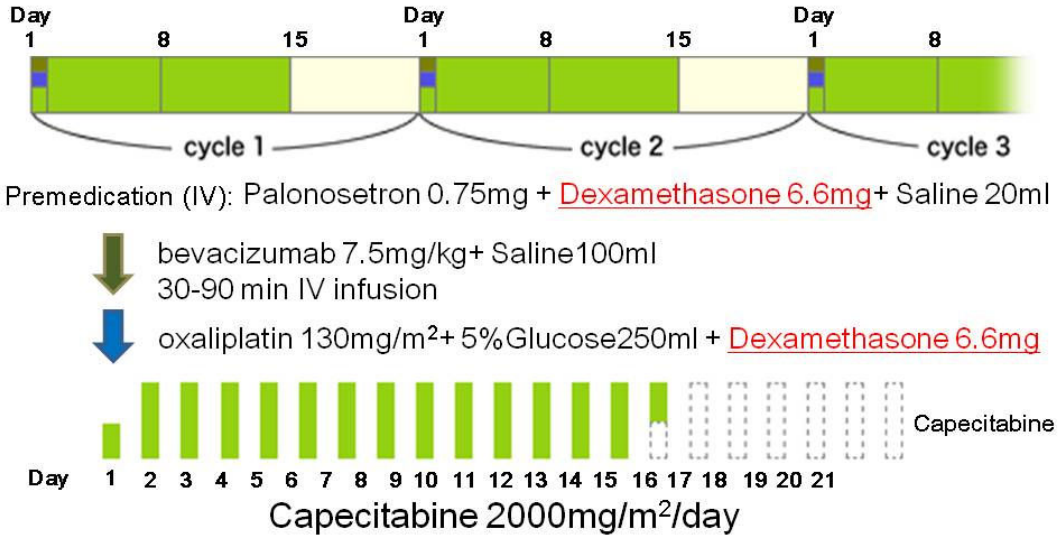

Fig. 1. XELOX+bevacizumab regimen as the first-line therapy in our hospital. Dexamethasone has been administered before and with oxaliplatin.

2.2 Chemotherapy Treatment

The study included 69 patients (44 men and 25 women; median age, 64 years) who received XELOX + bevacizumab therapy (bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m^2 on day 1, plus capecitabine 1000 mg/m^2 twice daily on days 1-14, every 3 weeks) for advanced or recurrent colorectal cancer without implantation of a CV port at the Department of Gastroenterological Surgery, Fukuoka University Hospital, between March 2010 and November 2011. In all the patients, oxaliplatin was administered in combination with DEX (6.6 mg) via the peripheral vein (Fig. 1).

2.3 Evaluation of Chemotherapy

We retrospectively reviewed clinical records of patients including characteristics (age, gender, ECOG PS, primary site, metastatic site), dosage, schedule of XELOX, and observed toxicities after the initial treatment. We also evaluated the confirmed response rate.

All patients underwent physical examination, chest radiography, and computed tomographic scans of the abdomen, pelvis, and chest before starting treatment at baseline. All patients were included in safety and efficacy analyses. The severity of adverse effects was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.0. Tumors were measured at 6- to 8-week intervals, and response was evaluated according to the response evaluation criteria for solid tumors (RECIST) version 1.1.

The evaluation of response was based on radiologist-reported measurements. Complete and partial response required subsequent confirmation of response after an interval of at least 4 weeks.

Table 1 shows the clinicopathological factors.

Table 1. Baseline characteristics of patients who received XELOX+bevacizumab therapy

Median age (range)	64 (40-87)
Male/Female	63.8/36.2%
ECOG PS 0/1	84.1/15.9%
Primary tumor	
Colon/Rectum	56.6/43.4%
Metastatic site	
Lung/Liver/Lung&Liver/others	8.7/36.2/13.0/42.1%
Oxaliplatin	1502 mg/body (498-4115)

2.4 pH of Infusion Solutions after Adding Dexamethasone

A commercial 250 mL of 5% glucose solution (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) with 208 mg of oxaliplatin (Yakult Honsha Co., Ltd. Tokyo, Japan) was used as the base solution. The pH was measured at 0, 1, 2, and 3 h in infusion solutions containing 3.3 mg or 6.6 mg of DEX (Fuji Pharma Co., Ltd., Shizuoka, Japan). The pH was measured with a pH meter (HM-30R, DKK-TOA; Tokyo, Japan).

3. RESULTS AND DISCUSSION

Between March 2010 and November 2011, we administered a XELOX regimen to 71 patients with metastatic CRC in a first-line treatment setting. Two patients were excluded according to the selection criteria. The excluded patients were a patient with an ECOG PS of 2 and a patient who had inadequate hematological, renal, and liver function.

Characteristics of the 69 selected patients included in this study are shown in Table 1. Their median age was 64 years. Median cumulative amount of oxaliplatin and number of cycles were 1502 mg/body and 7 cycles.

Among the patients, 84.1% had an ECOG PS of 0 at baseline and 43.5% of the patients had at least 2 organs involved, with the liver being the most common site of metastasis. Because most patients had synchronous metastatic disease at diagnosis, only 11 patients had received adjuvant therapy.

Vascular pain developed in 47 patients (68.1%), but it was transient. In only 1 of the 47 patients, the drip infusion route had to be switched to the opposite side (only once) because of vascular pain. Duration of vascular pain was an average 2.4 days (0-14), length of vascular pain was an average11.7 cm (5-30). No patients required CV port implantation or postponement of treatment due to adverse events caused by the administration of the drug via the peripheral vein. Grade 3 or higher hemotoxicity was noted in 14.5% of the patients, and grade 3 or higher nonhematological toxicity was noted in 20.3% of the patients (Table 2).

Table 2. Hematological and non-hematological adverse events of XELOX+bevacizumab therapy

	Hematological ≥ Grade3	Non-hematological ≥ Grade3
XELOX+bevacizumab (N=69, Median cycles 7)	14.5%	20.3%
	Neut:6	Diarrhea:4
	Plt:3	Ileus:2
	ALT:1	Cerebral infarction:2
		Ascites:1
		Pneumonia:1
		Hand foot synd:1
		Bone fracture:1
		Thrombosis:1
		Fournier's synd:1

The confirmed response rate was 59.4 % (Complete response: CR, 2.9%; Partial response: PR, 56.5%; Stable disease: SD, 40.6%; Progressive disease: PD, 0%). Surprisingly, among 69 patients, only one patient experienced hypersensitivity reactions (Cutaneous reaction) to oxaliplatin. Respiratory symptoms, ocular symptoms and anaphylaxis were not observed in 69 patients (Table 3).

Table 3. Hypersensitivity reactions

Characteristics	**N (%)**
Serious reactions	
Anaphylactic shock	0(0)
Immunologic thrombopenia	0(0)
Other reactions	
Respiratory symptoms	0(0)
Cutaneous reactions	1(1.4)
Generalized reactions	0(0)

Anaphylactic shock is defined as severe hypotension, associated with malaise and other symptoms as bronchospasm, erythema, pruit, Quincke edema, digestive symptoms. Respiratory symptoms include bronchospasm, laryngospasm, dyspnea. Cutaneous reactions include erythema, edema, Quincke edema, pruit,urticaria. Generalised reactions include fever, chills, malaise, sweats.

Table 4 shows the changes in pH at 0, 1, 2 and 3 h after adding DEX (3.3 mg or 6.6 mg) to 250 mL of infusion solution containing 135 mg/m^2 oxaliplatin. When 6.6 mg of DEX was added to this solution, the pH of the resulting solution was increased to 7.33. The pH after the addition of DEX 6.6 mg was less than 7.4 (Table 4).

Table 4. Changes in pH after adding DEX to 5% glucose solution containing oxaliplatin

	0 H	1 H	2 H	3 H
5%Glucose250ml oxaliplatin208mg DEX6.6mg	7.33	7.22	7.15	7.10
5%Glucose250ml oxaliplatin208mg DEX3.3mg	6.90	6.90	6.77	6.75
5%Glucose250ml oxaliplatin208mg	4.78	4.76	4.74	4.74

(pH meter: HM-30R, TOADKK)

Fonkalsrud et al. indicated that neutralizing the pH of the infusion solution to 7.4 significantly reduced the incidence of infusion phlebitis, and they concluded that neutralization of the infusion solution was the most significant factor for reducing infusion phlebitis (Fonkalsrud et al., 1968). Eremin et al. also showed that neutralizing to pH 7.0 significantly reduced the incidence of infusion phlebitis, and they concluded that neutralization enhanced the functional life span of the infusion (Eremin and Marshall, 1977). Although neutralizing to pH 7.4 is effective to prevent phlebitis, it may cause problems in the stability of the infusion solutions (Driscoll et al., 1994; Hill et al., 1996).

Many patients have experienced adverse effects such as phlebitis and venous pain, which have proved to be related to an unphysiologically low solution pH. Kuwahara et al., reported that phlebitis was less likely when the solution of Plas-amino was neutralized to pH 5.93 when given to rabbits, and was nearly eliminated when the pH was increased further to 6.49 (Kuwahara et al., 1996). Thus, the tolerance pH for the peripheral vein is about 6.5, i e, an infusion solution does not cause phlebitis due to acidity if the pH is not lower than the tolerance pH.

Corticosteroids have been suggested to be effective for the prevention of phlebitis owing to their antiinflammatory action (Polak, 1956; Kohlhardt, 1994; De Cock et al., 1984). Tononi et al. reported that posttreatment with DEX reduced phlebitis caused by vinorelbine (VNR) (Tononi et al., 1997), though they did not show the actual data. Thus, to demonstrate that corticosteroids can prevent the development of phlebitis after anticancer chemotherapy, they investigated the effects of DEX and PSL on VNR- and doxorubicin-induced phlebitis, respectively, in a rabbit model.

Kohno et al., have already shown that both rapid administration and dilution of the infusion solution is effective for preventing VNR-induced phlebitis (Kohno et al., 2008). In addition, the study suggested that pretreatment with DEX was more effective than posttreatment. Although the underlying mechanism by which DEX prevents phlebitis is not clear, it might be related to the well-known antiinflammatory effects of steroids. There have been a few reports that administration of steroids is useful for preventing irritation and phlebitis caused by intravenous infusion of hypertonic solutions in animals (Dubick and Wade, 2004). As mentioned above, there has only been 1 report that DEX can reduce phlebitis after the infusion of VNR, but without any evidence to support this claim (Tononi et al., 1997).

The causative factors of phlebitis include the pH and osmotic pressure of the solution, size of the vein used, size and material of the catheter, and infusion periods (Kuwahara et al., 1998).

The kinetics of the alkaline hydrolysis of oxaliplatin has been evaluated. Even though, at pH 7.4, the intermediate only constitutes a minor fraction (maximally 0.7%) of the oxaliplatin concentration, it might rapidly react with essential endogenous compounds resulting in a continuous conversion of oxaliplatin to its monodentate form (Jerremalm et al., 2003). As shown in Table 4, the pH did not exceed 7.4 even when DEX was added to oxaliplatin. Therefore, most of oxaliplatin does not appear to be degraded when administered in combination with DEX via the peripheral vein.

The XELOX regimen with DEX appears beneficial as the first-line therapy in recurrent or metastatic colorectal cancer, suggesting a controlled vascular pain with acceptable response rate. Oxaliplatin in 5% glucose is associated with less venous pain without decreasing oxaliplatin content although it is not generally recommended to dissolve oxaliplatin in a basic solution since it is unstable under alkaline conditions.

In addition to the review, there have been several case reports describing hypersensitivity reactions with oxaliplatin (Thomas et al., 2003). There is no difference in hypersensitivity reaction rates between FOLFOX and XELOX (Zhao et al., 2010). Hypersensitivity is broadly defined as a condition characterized by an exaggerated host response to the stimulus of a foreign antigen. Immediate hypersensitivity reactions (type I), also known as anaphylactic reactions, are initiated either by the combination of antigens with mast-cell-fixed cytophilic antibodies, or complement activation by antigen-antibody complexes that contain complement-fixing antibodies. Mast cell release of pharmacologically active substances leads to contraction of smooth muscles and dilation of capillaries in various organ systems. In sensitized patients, symptoms occur within minutes of antigen exposure, reach a peak within 1 h, and then rapidly recede. The affected systems include pulmonary (dyspnea, cough, rhonchi, wheezing), cardiovascular (rapid pulse, hypotension), mucocutaneous (itching, flushing, urticaria, angioedema, lacrimation, rhinorrhea), and gastrointestinal (difficulty swallowing, nausea, vomiting, diarrhea, cramps, bloating) functions. Non-IgE-mediated anaphylactoid reactions also occur, which are clinically indistinguishable from anaphylaxis, and result from drug- or chemical-mediated release of histamine from mast cells and basophils.

Table 5. Comparison with other studies of hypersensitivity reactions

Study	N	Hypersensitivity (%)	
		All	≥ Grade3
Brandi et al., 2003	124	13.7	7.3
Andre et al., 2004	1123	10.3	2.9
Gowda et al., 2004	169	19	<1 (G4)
Siu et al., 2006	180	15	2.2
Shibata et al., 2009	125	17	4
Seki et al., 2011	108	22.3	9.3
Our study	69	1.4	0

The incidence of allergic reactions to carboplatin and cisplatin is approximately 5% (Shebak et al., 1995). In the case of oxaliplatin, the incidence of severe anaphylactic reaction is estimated to be 0.5%, whereas the incidence of other hypersensitivity reactions in clinical practice is estimated to be 12% to 20% (Meyer et al., 2002; Brandi et al., 2003; Shibata et al., 2009; Kidera et al., 2011). These reactions are often self-limited but may be unpredictable. Recently, Kidera et al. reported that increased doses of DEX and antihistamine significantly reduced oxaliplatin-related hypersensitivity reactions from 20% to 7% (29). However, DEX has been administered as a premedication before the infusion of oxaliplatin. It may be coincidence, but we experienced only 1.4 % allergic to oxaliplatin. There is possibility that hypersensitivity reactions to oxaliplatin could have been prevented by co-infusion of DEX.

4. CONCLUSION

Addition of DEX to oxaliplatin drip infusion controlled the vascular pain caused by administration of oxaliplatin via the peripheral vein, enabling the continuation of XELOX therapy. The recorded response rate to this therapy combined with the use of DEX suggests that DEX probably does not exert adverse effects on the therapy, ie, it does not affect the stability of oxaliplatin by elevating the pH. Furthermore, co-infusion of DEX to oxaliplatin may be a useful preventive method for oxaliplatin-induced hypersensitivity. However, further studies will be needed to determine the efficacy of this method.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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