Drug-induced skin toxicity and clinical nursing of VitK cream on colorectal cancer patients

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Abstract: To discuss the impact of 0.1% vitamin K1 ($VitK_1$) cream on cetuximab-induced skin toxicity for colorectal cancer patients. 60 colorectal cancer patients with cetuximab therapy after hospitalization, were divided into experimental group (Ward A) and control group (Ward B) according to personnel sequential number, with 30 cases in each group. Routine nursing was implemented on control group. For experimental group, on the routine nursing basis, 0.1% $VitK_1$ cream was smeared on face, neck, chest, back and nail (toenail) edge with three times one day at the application of cetuximab day. After cetuximab applied in 8 weeks, both skin itch and dry skin for patients in experimental group were significantly improved compared those in control group, showing statistically significant difference (W=708.000, P=0.001: W=662. 500, P=0.000). 0.1% $VitK_1$ cream was conducive to improve both skin itch and dry skin symptoms in the cetuximab-induced skin toxicity for colorectal cancer patients.

Keywords: Vitamin K1; Cetuximab; skin toxicity; nursing.

INTRODUCTION

Cetuximab (C-225) is a new type of targeted drug in the therapy of cancer (Cunningham *et al*, 2014; Souglakos *et al*, 2008; Van *et al*, 2009; Bonner *et al*, 2010; Burtness *et al*, 2011; Bemier, 2010; Kim *et al*, 115; Rosell *et al*, 2013). Studies have reported that it has been widely applied in the treatment of colorectal cancer, gastric cancer, lung cancer and head and neck squamous cell carcinomas, either as combination drug or as single drug, which can enhance the effective rate of treatment, prolong the time to progressive disease, and improve patients' life quality (Zhen, 2010). It has been considered by Galizia *et al*. (2013) that on most patients, cetuximab is easily tolerant, without exacerbating the side effects from other chemotherapeutic drugs, and vice versa. However, cetuximab also has a certain particular side effects, such as skin toxicity (Tomkovd *et al*., 2013). The cetuximab-induced skin toxicity has the ability to seriously decline patients' life quality (Eilers *et al*, 2012 and Osio *et al*., 2013), as well as result in delays or interruptions in treatment. On medicine specification, it is definitely referred that when serious skin reaction is occurred in patients [America National Center of Tumor-Common Toxicity Criteria (NCT-CTC) = Grade 3], the cetuximab treatment must be interrupted. Only the reaction is relieved into Grade 2, the treatment can be proceeded. Therefore, in order to ensure the continuous effective treatment, the improvement in patients' survival rate and life quality, the prevention and control on skin toxicity are very crucial (Segaert and Van, 2014 and Hetherington *et al*, 2013). Plenty of clinical experiments abroad have verified that 0.1% $VitK_1$ cream for external use is able to effectively relieve the cetuximab-induced skin toxicity (Ocvirk and Rebersek, 2010; Ocvirk and Rebersek, 2012; Radovics *et al*, 2013; Pinto *et al*, 2011). Due to this cream has not been listed in China, neither reports on the effects and corresponding assessment to adverse effects, this study is intended to discuss the impact of 0.1% $VitK_1$ cream for external use on cetuximab-induced skin toxicity for colorectal cancer patients in China, expecting to verify the applicability of $VitK_1$ cream on cetuximab-induced skin toxicity for patients in China and find out the suitable cure methods for cetuximab-induced skin toxicity, with support and assurance for the treatment completion for patients.

MATERIAL AND METHODS

Subjects

Sixty colorectal cancer patients with cetuximab therapy after hospitalized in The First Affiliated Hospital of Zhengzhou University from January 2013 to October 2014 were selected and divided into experimental group (Ward A) and control group (Ward B) according to personnel sequential number, with 30 cases in each group.

Inclusion criteria: Those with informed consent; those in at least 20 years age; those with C-225 treatment for the first time; Those with the therapeutic regimen of cetuximab plus FOLFOX4/14 days and cetuximab plus FOLFIRI/ 14 days. Exclusion criteria: those with skin disease before cetuximab therapy; those with diabetes. In ages, genders, diagnoses and regimens, no statistically significant difference was shown for patients in both two groups (P>0.05), with details in table 1.

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Disposal methods

Routine nursing was implemented for patients in both two groups. In experimental group, at the application of cetuximab day, 0.1% $VitK_1$ cream was smeared on face, neck, chest, back and nail (toenail) edge by charge nurses with three times one day at 9am. 3pm and 9pm. The cream was covering the above mentioned skin sites. That the cream was covering above skin and smeared to no visible until the cream was unabsorbed was as the amount standard. The charge nurses participating into research had an unified training by researchers.

Due to this cream had not been listed in China, the drug manufacturing room of Institute of Materia Medica, Chinese Academy of Medical Science was authorized to prepare VitK1 cream with drafted prescription. The main component was 0.1% $VitK_1$, with the rest of routine excipients for emulsifiable paste. The excipients component included: (1) glycerin monostearate (ointment bases and stabilizer, making products smoothingly); (2) stearic acid (hydrophilic ointment bases); (3) liquid paraffin (Adjusting the ointment consistency); (4) Vaseline (Enhancing Water absorption together with lanolin); (5) Lanolin (with property close to the sebum, easy to penetrate the skin, suitable for drugs required to absorb); (6) sodium lauryl sulfate (anionic emulsifier); (7) nipagin (common bacteriostatic agent in soft stalk); (8) triethanolamine (emulsifier, pH regulator); (9) distilled water (oil-in-water ointment diluent). The finished product was oil-in-water emulsifiable paste, in white paste, 10g/ per branch, with strong affinity to skin surface, without influence on skin's original functions. After smeared, it could cover the skin surface, with the function to improve the dry skin.

Evaluation methods

On the second day after the fourth cycle finished with the application of cetuximab, through the utilization of the assessment section of skin adverse event in NCT-CTC 3.0, skin toxicity for patients between experimental group and control group were evaluated. NCT-CTC 3.0, published on August 9th, 2006, was the currently most common evaluation criteria to evaluate cetuximab-induced skin toxicity (National Cancer Institute). Meanwhile, the evaluation on the requirement for drug discontinuance by skin toxicity in cetuximab Chinese-edition specification was also applied that criteria.

STATISTICAL ANALYSIS

SPSS 19.0 statistical software was used for handling all information. Wilcoxon rank-sum test was adopted for intergroup difference. $P<0.05$ was considered statistical significance.

RESULTS

The comparison profiles on acne-like rash, dry skin, skin itch, skin dehiscence, paronychia and photosensitivity for patients in two groups were shown in table 2.

Dry skin

Dry skin with no less than Grade 4 was not occurred for patients in both experimental group and control group. The occurrence rates of dry skin in Grade 0-3 in experimental group were 16.7%, 66.7%, 16.7% and 0 respectively; while those in control group were 10%, 13.3%, 73.3% and 3.3% respectively. Distinct improvement in dry skin was shown for patients in experimental group compared that in control group, with statistically significant difference (W=708.000, P=0. 001).

Skin itch

Skin itch with no less than Grade 4 was not occurred for patients in both experimental group and control group. The occurrence rates of skin itch in Grade 0-3 in experimental group were 43.3%, 50%, 6.7% and 0 respectively; While those in control group were 30%, 13.3%, 53.3% and 3.3% respectively. Distinct improvement in skin itch was shown for patients in experimental group compared that in control group, with statistically significant difference (W=662.500, P=0.000).

Acne-like rash, skin dehiscence and paronychia

Acne-like rash with no less than Grade 4 was not occurred for patients in both experimental group and control group.

Table 1: Comparison in general information for patients in two groups

Item	Experimental group (n=30)	Control group (n=30)	t/x^2	P value
Gender Male Female	 26 (86.7) 4 (13.3)	 20 (66.7) 10 (33.3)	3. 354	0. 067
Diagnosis			0. 067	0. 796
Rectal cancer	16 (53.3)	15 (50)		
Colon cancer	14 (46.7)	15 (50)		
Regimen			0. 000	1.000
Cetuximab + F0LFIRI	13 (43.3)	13 (43.3)		
Cetuximab+ F0LF0X4	17 (56.7)	17 (56.7)		
Age (Years, X ± s)	52.23±10. 94	56.20±10. 58	1.428	0.159

Table 2: Severity situation of skin toxicity in patients between two groups [cases(%)]

Item	Experimental group	Control group	W value	*P* value
Acne-like rash			885.500	0.642
Grand 0	0	0		
Grand 1	12(40)	11(36.7)		
Grand 2	11(36.7)	10(33.3)		
Grand 3	7(23.3)	3(30)		
Grand 4	0	0		
Grand 5	0	0		
Dry skin			662.500	0.000
Grand 0	5 (16.7)	3 (10)		
Grand 1	20 (66.7)	4 (13.3)		
Grand 2	5 (16.7)	22 (73.3)		
Grand 3	0	1 (3.3)		
Grand 4	0	0		
Grand 5	0	0		
Skin itch			708.000	0.001
Grand 0	13 (43.3)	9 (30)		
Grand 1	15 (50)	4 (13.3)		
Grand 2	2 (6.7)	16 (53.3)		
Grand 3	0	1 (3.3)		
Grand 4	0	0		
Grand 5	0	0		
Skin dehiscence			870.000	0.284
Grand 0	27 (90)	24(80)		
Grand 1	1 (3.3)	2 (6.7)		
Grand 2	2 (6.7)	4 (13.3)		
Grand 3	0	0		
Grand 4	0	0		
Grand 5	0	0		
Paronychia			829.000	0.139
Grand 0	21 (70)	16 (53.3)		
Grand 1	8 (26.7)	10 (33.3)		
Grand 2	1 (3.3)	4 (13.3)		
Grand 3	0	0		
Grand 4	0	0		
Grand 5	0	0		

The occurrence rates of acne-like rash in Grade 0-3 in experimental group were 0, 40%, 36.7% and 23.3% respectively; while those in control group were 0, 36.7%, 33.3% and 30% respectively. There was no statistically significant difference between groups (W=885.500, P= 0. 642). It could be observed that the occurrence rate of acne-like rash in Grade 2-3 for patients in experimental group was smaller than that in control group.

Skin dehiscence with no less than Grade 3 was not occurred for patients in both experimental group and control group. The occurrence rates of skin dehiscence in Grade 0-2 in experimental group were 90%, 3.3% and 6.7% respectively; while those in control group were 80%, 6.7% and 13.3% respectively. There was no statistically significant difference between groups (W= 870.000, P=0. 284). That the occurrence rate of skin dehiscence in Grade 1-2 for patients in experimental group was smaller than that in control group could be observed.

Paronychia with no less than Grade 3 was not occurred for patients in both experimental group and control group. The occurrence rates of paronychia in Grade 0-2 in experimental group were 70%, 26.7% and 3.3% respectively; while those in control group were 53.5%, 33.3% and 13.3% respectively. There was no statistically significant difference between groups (W=829.000, P= 0. 139). That the occurrence rate of paronychia in Grade 1-2 for patients in experimental group was smaller than that in control group could be observed.

Toxic and side effect

The application time of observed 0.1% $VitK_1$ cream in

this study was 56 days. In this study stage, skin redness and swelling, ulceration and other adverse effects were not observed. Discomfort by cream was not told from patients.

DISCUSSION

Necessity to intervene cetuximab-induced skin toxicity

Cetuximab is a type of targeted drug, with strong specificity and little side effects, showing more advantage than traditional chemotherapeutic drugs (Xiong and Xiang, 2013). Cetuximab-induced skin toxicity has the ability to seriously affect patients' physical, psychological and social activities, thus finally leading to therapy interruption or the decline in drug dosage. Therefore, experts advise that in the process of cetuximab treatment, it is necessary to intervene skin toxicity occurrence (Pinto *et al*, 2013).

Feasibility of 0.1% VitK$_1$ intervening cetuximab-induced rash

Cetuximab is an epider-mal growth factor receptor (EGFR) inhibitor, while EGFR plays a crucial role in both growth and function of normal skins (Vallbohmer and Lenz, 2012). After the application with this EGFR inhibitor treatment, the normal expression channel of EGFR is interdicted, resulting in the abnormal growth, differentiation and maturity of skin and resistance to cell migration formed by cutin, thus apoptosis on epidermis cells, with the expression of atrophy of epidermis, disappearance of hair follicle structure and crack in skins (Mitchell *et al*, 2013). Studies have confirmed that Vitamin K is a EGFR activator, which not only can rescue the skin toxicity induced by cetuximab but also enable directly act on skin for external use with minimum absorption (Perez-Soler *et al*, 2011). The average occurrence rate of skin toxicity can be decreased to 64.4% from 85% in the past. At the same time, the occurrence rate at serious skin toxicity is decreased into 0 from 3%-17% in the past. Those help to effectively reduce the occurrence strength and frequency of skin toxicity, without VitK$_1$ adverse effect found.

Intervene effect of 0.1% VitK$_1$ on cetuximab-induced skin toxicity

The occurrence rate of skin toxicity observed in this study was 100% (both experimental group and control group). The observed skin toxicity included acne-like rash, dry skin, skin itch, skin dehiscence, paronychia and photosensitivity. Recently, the study that the cetuximab-induced skin itch can affect patients' life has not been reported. Study by Fusheng Ma (Ma *et al*, 2010) *et al* has indicated that the more serious in itch symptom for skin disease patients, the greater negative influence on their psychology, sport, work, study, sleep and social interaction and entertainment. Meanwhile, the mutual promotion and mutual effect are affecting in patients' psychological factors and sleep disorders. Moreover, in the process of applying cetuximab, the release of inflammatory medium can be stimulated, secondary infection will be occurred upon serious skin reaction and infection symptoms may be accelerated or exacerbated by scratch due to itching. Those suggest that it is necessary to control the cetuximab-induced skin itch symptoms. The results in this study showed that the intervention through 0.1% VitK$_1$ has the ability to improve cetuximab-induced skin itch, statistical significance shown in difference between groups (P=0.004). That was consistent of the research results by Pinto *et al*. (2011).

Dry skin often covers the finger (toe) tip in fingers and toes, periungual skin and digital joints, partial sites showing dry scale-like eczema. Furthermore, staphylococcus aureus is able to occur successively, together with acute exudative epidermitis and yellow scabs. Besides skin, oral mucosa, nasal mucosa, vaginal mucosa and other mucosal tissues also often have the dry symptoms. If it is serious, the patients' daily activity and sleep will be affected, causing patients' psychological burden. Therefore, improvement in cetuximab-induced dry skin may be conducive to improve patients' life quality. The results in this study showed that the intervention through 0.1% VitK$_1$ has the ability to improve cetuximab-induced dry skin, statistical significance shown in difference between groups (P= 0.000).

The convenience sampling method was adopted in this study, with a few cases. Sample volume should be expanded for the further verification to the study results. This study indicated that in the serious degree of external 0.1% VitK$_1$ intervention to alleviate cetuximab-induced acne-like rash, no statistical significance was shown in difference between groups (P=0.642), showing different from the successive 5 reports during 2008 to 2011 by Ocvirk, Radovics and Pinto *et al* (Ocvirk and Rebersek, 2010; Ocvirk and Rebersek, 2012; Radovics *et al*, 2013; Pinto *et al*, 2011), but consistent with the recent report result by Horg *et al*. Therefore, further discussion on this aspect is still needed.

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