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C-reactive protein levels and 5-Fu induced oral mucositis in colorectal cancer patients chemotherapy with 5-fluorouracil based regimens

Valutazione dei livelli di proteina C-reattiva e mucositi orali indotte da 5-Fluorouracile (5-Fu) in pazienti con cancro colon rettale sottoposti a chemioterapia con regimi di 5-Fu

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Summary

Aims: **The aim of this study was to evaluate the relationship between C–reactive protein (CRP) levels and the grade of 5–Fu induced oral mucositis in colorectal cancer patients chemotherapy with 5-fluorouracil based regimens.** ***Materials and Methods:*** **This study was performed in 47 patients treated with 5-fluorouracil based regimens. Serum CRP levels were initially tested on the day before chemotherapy. Subsequently the serum CRP levels were measured on the second day during chemotherapy, on the first day after chemotherapy, on the second day after chemotherapy and on the third day after chemotherapy. Oral mucositis**

Riassunto

Finalità: **Valutare la relazione tra i livelli di proteina C-reattiva (C–reactive protein, CRP) e il grado di mucositi orali indotte da 5-Fu in pazienti con cancro colon rettale sottoposti a chemioterapia con regimi di 5-Fu.** ***Metodi e Materiali:*** **Lo studio è stato condotto su 47 pazienti trattati con regimi di 5-fluorouracile. Inizialmente, i livelli di CRP sierica sono stati testati il giorno antecedente l'inizio della chemioterapia. In seguito, i livelli di CRP sierica sono stati misurati nel secondo giorno di chemioterapia, il primo giorno, il secondo giorno e il terzo giorno dopo la fine della chemioterapia. Le mucositi orali sono state analizzate dagli oncologi su campioni di sangue prelevato**

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were evaluated by oncologists on days of blood sampling. *Results:* The distribution of the most severe mucositis was Grade I mucositis in 17.0% (8) of the patients, Grade II in 14.9% (7) of the patients and Grade III in 10.6% (5) of the patients. Statistical analysis indicated a significant rise in the CRP levels (p<0.001) according to the course of chemotherapy and grade of oral mucositis. A change of the mean CRP levels was correlated with progression of mean grade of oral mucositis according to the course of chemotherapy. *Conclusions:* A significant relationship between the presence of 5-Fu induced oral mucositis and CRP levels in this study was observed. The CRP levels could be conveniently determined along with the evaluation of mucosal reactions during or after chemotherapy to provide further information on 5-Fu induced oral mucositis. Eur. J. Oncol., 17 (2), 87-92, 2012

Key words: **C–reactive protein, 5-Fu, chemotherapy, oral mucositis, colorectal cancer.**

in giorni diversi. *Risultati:* Le mucositi più gravi sono così distribuite: mucositi di Grado I nel 17,0% (8) dei pazienti, di Grado II nel 14,9% (7) dei pazienti e di Grado III nel 10,6% (5) dei pazienti. L'analisi statistica mostra una crescita significativa nei livelli di CRP (p< 0.001) durante il corso della chemioterapia e a seconda del grado della mucosite orale. Un cambiamento dei livelli medi di CRP è correlato alla progressione del grado medio delle mucositi orali durante il corso della chemioterapia. *Conclusioni:* Questo studio ha dimostrato una correlazione significativa tra la presenza di mucositi orali indotte da 5-Fu e i livelli di CRP. Per ottenere maggiori informazioni sulle mucositi orali indotte da 5-Fu, sarebbe opportuno determinare i livelli di CRP valutando le reazioni della mucosa durante o dopo la chemioterapia. Eur. J. Oncol., 17 (2), 87-92, 2012

Parole chiave: **Proteina C-reattiva, 5-Fu, Chemioterapia, Mucosite orale, Cancro colon rettale.**

Introduction

Chemotherapy-induced mucositis increasingly has become a common dose-limiting toxicity for a number of regimens. Chemotherapeutic agents, such as 5-fluorouracil (5-FU), are commonly used in the treatment of many breast and intestinal cancers, acting by inhibition of cell division processes resulting in reduced cellular proliferation (1). Approximately 80% of patients receiving 5-Fu therapy experience mucositis. Oral mucositis and the associated emergence of inflammatory-like changes at various locations of the oral cavity has been reported to complicate the course in up to 40% of patients receiving standard cytotoxic chemotherapy particularly including 5-fluorouracil (5-FU)-based regimens (2).

The presence of mucositis-associated lesions may necessitate interruption of treatment, reduction of dose of chemotherapeutic agents and affect the patients' compliance with other prescribed medications. Oncologists thus need to consider the appearance and change in grade of chemotherapy–induced mucositis. It has been speculated that mucositis results from a process that includes changes in endothelium and connective tissue, as well as epithelium, which is stimulated by a number of cytokines (3). The serum concentration of the acute phase reactant C-reactive protein (CRP) is raised in inflammatory reactions and tissue destruction (4). We hypothesized that serum CRP levels might be related to 5-Fu induced oral mucositis, because oral tissue necrosis would induce an acute phase reaction that could be quantified by serial measurement of CRP concentrations. It would be useful for chemotherapy oncologists to assess 5-Fu induced oral mucositis with changes in CRP levels. We evaluated the relationship between change in serum CRP levels and the course or degree (i.e., severity) of 5-Fu induced oral mucositis in colorectal cancer patients chemotherapy with 5-fluorouracil based regimens.

Materials and methods

Patients

This study was designed to enroll primary colorectal cancer patients who received adjuvant

chemotherapy with 5-Fluoroacil based regimens between January 2008 and December 2010. The primary sites of cancer were the colon and rectum. Clinical stages of all cases were classified according to the American Joint Committee on Cancer staging system (sixth edition) using a physical examination and imaging study. Some patients on a concurrent chemoradiotherapy (CCRT) protocol were excluded to rule out the impact of radiotherapy on acute phase reactions and radiation-induced mucositis. All of whom did not received prior chemotherapy or concurrent radiotherapy. The inclusion criteria of our study included the following ones: age older than 18 years, Eastern Cooperative Oncologic Group (ECOG) performance status p1, normal function tests for hematology, renal, and liver. Patients were all required to be free of any signs of systemic infection, and must not have taken antibiotics or consumed alcohol for at least 1 week before testing, and were not allowed to have taken non-steroidal anti-inflammatory drugs during the 2 weeks before and during the CRP test. Informed consent was obtained from all patients.

This trial protocol was approved by the Institutional Review Board of our hospital.

Chemotherapy

Eligible patients, all of whom had histologically confirmed advanced or metastatic cancer, received FOLFOX6 (folinic acid, 5-FU, and oxaliplatin)/ FOLFIRI (folinic acid, 5-FU, and irinotecan) regimen chemotherapy. Patients had not received the chemotherapy previously. Chemotherapy consisted of a 2-hour infusion of levoleucovorin 200 mg/m^2 followed by a 5-FU bolus 400 mg/m^2 and 46-hour infusion 2,400 to 3,000 mg/m^2 every 46 hours every 2 weeks, either with irinotecan 180 mg/m^2 or with oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1.

Analysis of CRP level

Serum CRP levels were initially checked on the day before chemotherapy. Subsequently the serum CRP levels were measured on the second day during chemotherapy, on the first day after chemotherapy, on the second day after chemotherapy and on the third day after chemotherapy. Blood sampling was performed at dawn. Serum CRP was measured by latex agglutination using CRP-L kit (Sigma-Aldrich Co. Ltd. America).

Analysis of acute mucositis

Mucosal reactions, especially the posterior aspect of the tongue and most parts of the oropharynx, were examined and described on days of blood sampling before, during and after chemotherapy. Acute mucositis was grossly and endoscopically evaluated by 1 oncologist according to the use of the World Health Organization (WHO) Oral Toxicity Scale and was confirmed by a second oncologist. Each evaluation was independent. In the case that the 2 observers evaluated the grade of mucositis differently in the same patient, the higher grade was chosen.

The WHO criteria for oral mucositis from chemotherapy are the following ones: Grade 0=none; Grade 1=soreness and/or erythema; Grade 2= erythema, ulcers, and patient can swallow solid food; Grade 3=ulcers with extensive erythema and patient can not swallow solid food; and Grade 4=mucositis to the extent that alimentation is not possible.

Statistical analysis

The Kruskal–Wallis H test was used for the analysis of the relationship between changes in CRP levels and the grade of 5-Fu induced mucositis. Statistical analysis for the correlation between the day before, during and after chemotherapy and the serum concentration of CRP or the grade of mucositis was determined by use of the paired t test. Mean values of the CRP levels and grade of mucositis according to the day before, during and after chemotherapy were used, instead of each maximum value, to evaluate the positive correlation. Statistical analyses were performed with SPSS 13.0 software (SPSS Inc., Chicago, IL) and GraphPad Prism 5 (GraphPad Software, Inc.). A p value of less than 0.05 was regarded as statistically significant.

Results

A total of 47 patients underwent the chemotherapy schedules. The patients underwent three times

testing of CRP levels , and mucosal reactions were evaluated. Characteristics of the patients are summarized in Table 1. The duration of chemotherapy was four days (including the days before and after chemotherapy). Mean C-reactive protein (CRP) levels according to the day before, during and after chemotherapy are indicated in Table 2. Forty-three percent (20 patients) of all participants developed at least one episode of oral mucositis during chemotherapy. Using the WHO criteria, the severity of oral mucositis during chemotherapy was 57.4% (27) grade 0, 17.0% (8) grade 1, 14.9% (7) grade 2, 10.6% (5) grade 3, and 0% (0) grade 4. The mean grade of oral mucositis as a function of chemotherapy day significantly increased during the chemotherapy schedule ($p<0.001$; Figure 3).

The CRP levels showed a significant increase by the day before, during and after chemotherapy. The CRP levels during chemotherapy are shown in Table 2. Mean CRP levels significantly increased during the course of chemotherapy ($p<0.001$); mean CRP level in accordance with the grade of oral mucositis are shown in Table 3. Statistical analysis demonstrated a significant rise in the mean value of the CRP level ($p<0.001$) according to the day before, during and after chemotherapy and the grade of oral mucositis (Figs. 1 and 2). Figure 3 shows that the

Table 1 - Characteristics of the study patients

Characteristic	Patients (N=47)	%
Median age, y (range)	58 (45-72)	
Male:female	33:14	
Site, colon:rectum	34:12	
Dukes staging		
B (T3,N0,M0 at high risk for systemic recurrence or T4,N0,M0)	10	21
C	31	66
D	6	13

Table 2 - Mean C-reactive protein (CRP) levels according to the day before, during and after chemotherapy

The course of chemotherapy	CRP levels (mean±SD, mg/dl)
The day before chemotherapy	0.47±0.11
The second day during chemotherapy	1.02±0.30
The first day after chemotherapy	2.11±0.25
The second day after chemotherapy	1.49±0.16
The third day after chemotherapy	0.79±0.16

SD=standard deviation

Table 3 - Mean C-reactive protein (CRP) levels according to grade of oral mucositis

Grade	CRP levels (mean±SD, mg/dl)
0	0.46±0.02
1	0.94±0.13
2	1.59±0.09
3	2.14±0.16

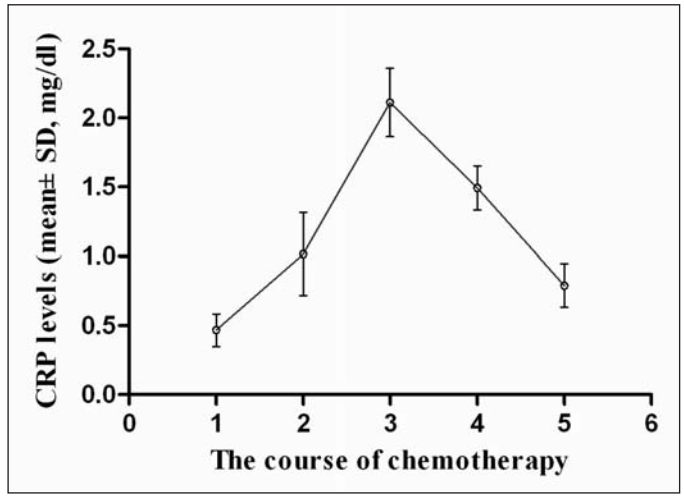

Fig. 1. Changes in CRP levels (mean±SD) according to the course of chemotherapy. 1=the day before chemotherapy; 2=the second day during chemotherapy; 3=the first day after chemotherapy; 4=the second day after chemotherapy; 5=the third day after chemotherapy.

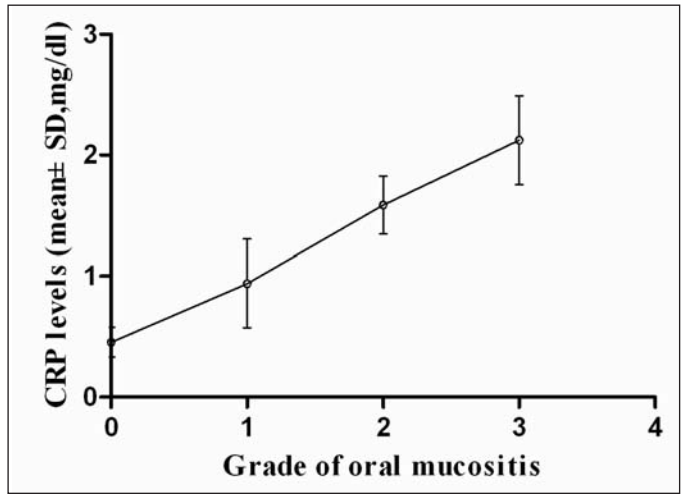

Fig. 2. Changes in CRP levels (mean±SD) according to grade of oral mucositis

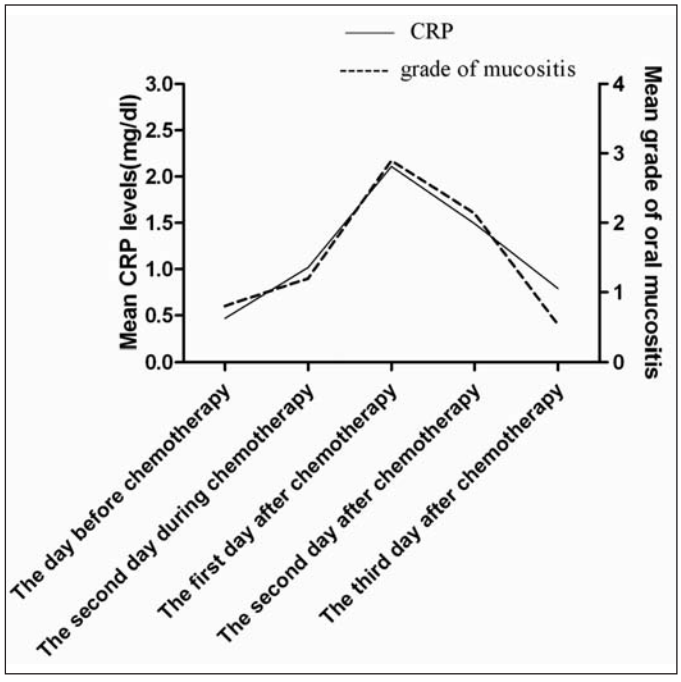

Fig. 3. Mean C–reactive protein (CRP) levels and mean grade of oral mucositis determined according to the course of chemotherapy

change in mean level of CRP was correlated with progression of the mean grade of oral mucositis according to the day before, during and after chemotherapy. As the mean grade of oral mucositis increased or decreased, the mean CRP levels changed nearly simultaneously (correlation coefficient=0.954, $p<0.001$).

Discussion

Colorectal carcinoma is a frequently occurring malignancy particularly affecting the elderly population (5-6). The fluorinated pyrimidine 5-fluorouracil (5-FU) is presently the most effective and frequently used antineoplastic agent for the treatment of advanced or metastatic colorectal cancer (7). Oral mucositis is a common dose-limiting toxic effect of chemotherapy, especially fluoropyrimidines (5-Fu, etc.), anthracyclines, and folate-based drugs such as methotrexate (8). Although oral mucositis is usually not life-threatening, it can cause severe pain and may have a significant impact on patient nutrition and quality of life. In some cases, the oral mucositis and associated discomfort are so severe that chemotherapy is reduced or discontinued. This can compromise patient prognosis. The frequency of oral mucositis varies with chemotherapy protocols and malignancy. Reports of 5-FU induced oral mucositis range from 8 to 89% for colorectal cancers (7). Routine screening for oral mucositis is not available for many cancer patients receiving chemotherapy.

Some studies reported that the serum concentration of the acute phase reactant C-reactive protein (CRP) is raised in inflammatory reactions and tissue destruction (4). Information on 5-fluorouracil based-chemotherapy induced inflammation may provide details on the relationship with the acute phase reactants. We planed to evaluate the severity of 5-Fu induced oral mucositis and the change in the CRP levels in colorectal cancer patients treated with 5-fluorouracil based regimens, and also aimed to determine a possible correlation between serum CRP levels and the course of oral mucositis. The serum levels of CRP showed an increasing trend with the course of chemotherapy, which indicated a statistically significant correlation between the course of chemotherapy and the grade of 5-Fu induced oral mucositis. Our results also showed that the mean value of CRP levels increased similarly with the mean grade of oral mucositis during the course of chemotherapy.

The level of CRP is often measured in cases of inflammatory disorders for monitoring a course and an effect of therapy. A significant relationship between the CRP levels and oral mucosal reaction in our study was observed. The World Health Organization classification has been a commonly used scale in chemotherapy oncology (9-10). However, this grading system is occasionally ambiguous for accurately classifying the grade and for predicting the course of oral mucositis.

Our study demonstrated that the CRP levels increased in the course of chemotherapy and decreased after chemotherapy, and showed that the change of the mean CRP levels was correlated with the progression of the mean grade of oral mucositis. Therefore, taking the CRP levels into account, evaluating the patients'oral mucosal reactions during or after chemotherapy is helpful to provide information on 5-Fu induced oral mucositis. Ki Y *et al.* reported that a significant correlation between the acute mucositis and CRP level in patients who received intensity-modulated radiation therapy as a radical

treatment of primary laryngo-pharyngeal cancer was present (11). Moreover, in our study a significant correlation between oral mucositis and CRP levels was observed. However, these findings do not insure that the levels of CRP exactly represent the grade of 5-Fu induced oral mucositis, because the CRP levels are affected by many factors or conditions such as concurrent tumour, secondary infection, gastrointestinal disease problems, or concurrent treatment (12). Thus, 5-Fu induced inflammatory mucosal reaction might be a key factor inducing the rise of CRP levels in this study. Moreover, whether we could readily apply these results to an individual patient is still in doubt. To evaluate the statistical correlation between change of CRP levels and 5-Fu induced oral mucositis in all individual patients simultaneously is very difficult, and using grade of mucositis and mean values of CRP levels involves a great deal of patient to patient variation.

Conclusions

In conclusion, a significant correlation between the presence of 5-Fu induced oral mucositis and CRP levels in this study was observed. Nevertheless, we need to carry out further research in the near future so that we could obtain more concrete and individualized information. We plan to evaluate other factors related to 5–Fu induced oral mucositis, such as concurrent therapy (7, 13).

References

1. Hejna M, Köstler WJ, Raderer M, *et al.* Decrease of duration and symptoms in chemotherapy-induced oral mucositis by topical GM-CSF: results of a prospective randomised trial. Eur J Cancer 2001; 37(16): 1994-2002.
2. Cool JC, Dyer JL, Xian CJ, *et al*. Pre-treatment with insulin-like growth factor-I partially ameliorates 5-fluorouracil-induced intestinal mucositis in rats. Growth Horm IGF Res 2005; 15(1): 72-82.
3. Sharma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol 2005; 6(2): 93-102.
4. Milroy R, Shapiro D, Shenkin A, *et al.* Acute phase reaction during chemotherapy in small cell lung cancer. Br J Cancer 1989; 59(6): 933-5.
5. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. N Engl J Med 2009; 361(25): 2449-60.
6. Crespi M, Lisi D. Colorectal cancer: a spreading but preventable disease. Eur J Oncol 2008; 13(1): 21-32.
7. McCarthy GM, Awde JD, Ghandi H, *et al.* Risk factors associated with mucositis in cancer patients receiving 5-fluorouracil. Oral Oncol 1998; 34(6): 484-90.
8. Keefe DM, Schubert MM, Elting LS, *et al.* Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007; 109(5): 820-31.
9. Awidi A, Homsi U, Kakail RI, *et al.* Double-blind, placebo-controlled cross-over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer. Eur J Cancer 2001; 37(16): 2010-4.
10. Wuketich S, Hienz SA, Marosi C. Prevalence of clinically relevant oral mucositis in out patients receiving myelosuppressive chemotherapy for solid tumors. Support Care Cancer 2012; 20(1): 175-83.
11. Ki Y, Kim W, Nam J. C-reactive protein levels and radiation-induced mucositis in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009; 75(2): 393-8.
12. Sonis S, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. Oncology (Williston Park) 1991; 5(12): 11-8.
13. Herlofson BB, Norman-Pedersen K, Redfors M, *et al*. Oral mucosal side effects of cytotoxic chemotherapy of testicular cancer. A retrospective study. Eur J Oral Sci 1997; 105(5 Pt 2): 523-6.