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ORIGINAL ARTICLE

Carcinoembryonic antigen surge in metastatic colorectal cancer patients responding to irinotecan combination chemotherapy

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Abstract

Background and objective: Oxaliplatin (OXA)-induced carcinoembryonic antigen (CEA) surge was reported to be associated with a clinical benefit. The aim of this study was to investigate the phenomenon of CEA surge in irinotecan-based chemotherapy.

Methods: We retrospectively reviewed 132 patients with metastatic colorectal cancer treated with irinotecan-based chemotherapy. Incidence of a CEA surge and chemotherapy efficacy were investigated.

Results: Eleven of 99 eligible patients (11.1%) had CEA surges. None of the 11 patients showed progressive disease (four had a partial response, seven had stable disease).

Conclusion: A CEA surge can be induced by irinotecan-based chemotherapy. An early increase in CEA after irinotecan-based chemotherapy does not usually indicate progression of disease and failure of therapy, and should not lead to a change of chemotherapy.

Keywords: *Carcinoembryonic antigen surge; chemotherapy; irinotecan; metastatic colorectal cancer*

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide. Approximately 50% of the patients with CRC develop metastases and eventually die (Jemal et al. 2005). Palliative chemotherapy is more effective than best supportive care at prolonging survival and improving quality of life (Meyerhardt & Mayer 2005). First-line therapy of metastatic colorectal cancer (MCRC) is now based on oxaliplatin (OXA) or irinotecan administered in combination with leucovorin (LV) and 5-fluorouracil (5-Fu) (Tournigand et al. 2004), alongside the introduction of biologic therapies (Cunningham et al. 2004, Saltz et al. 2008). Assessment of treatment efficacy is based mainly on radiological examination about every 2 months during the course of treatment in order to identify disease progression and allow for modifications of the chemotherapy regimen. The American Society of Clinical Oncology (ASCO) also recommends carcinoembryonic antigen (CEA) as the marker of choice for monitoring MCRC during systemic therapy (Locker et al. 2006). Generally, a rise in CEA level indicates tumour progression. However, two studies (Sorbye & Dahl 2004, Ailawadhi et al. 2006) have reported a transient increase in CEA level despite an objective response among MCRC patients treated with OXA combination chemotherapy. Therefore, the 'ASCO 2006 update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer' has mentioned the possibility of a CEA surge between the 4th and 6th week of a new therapy, especially after

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the OXA regimen (Locker et al. 2006). Previous results from our institution have demonstrated this phenomenon occurring in Chinese patients with MCRC treated with OXA combination chemotherapy (Li et al. 2009). Moreover, our study also showed a transient CEA surge in three out of 49 patients treated with irinotecan-based combination chemotherapy; however, such a CEA surge phenomenon has not been previously demonstrated. Therefore, the aim of this study was to evaluate further the incidence of CEA surge in MCRC patients treated with irinotecan-based combination chemotherapy and its relevance to clinical outcome.

Patients and methods

Patients

We retrospectively reviewed the medical records of MCRC patients treated with irinotecan-based combination chemotherapy (FORFIRI or XELIRI regimen) at Sun-Yat Sen University Cancer Center from July 2004 to August 2008. The eligibility criteria for inclusion in the study were: (1) adenocarcinoma of the colon or rectum; (2) a Karnofsky Performance Status (KPS) score ≥80; (3) normal liver and renal function, and evaluable metastatic disease; (4) a pretreatment baseline serum CEA concentration >5 ng ml^{-1}; (5) serial monitoring of CEA level throughout the treatment. Patients who had received the irinotecan-based combination chemotherapy were eligible if it was used as either first-line or second-line treatment. Written informed consent was signed before treatment.

Methods

Data obtained included age, sex, tumour pathology, metastatic sites, type of treatment, response evaluation, and baseline and serial levels of CEA throughout the treatment. Serum CEA concentration was measured by a commercially available enzyme immunoassay Elecsys CEA assay (Roche, Germany). For each patient, the serum CEA level was analysed at baseline and thereafter 1 day before each chemotherapy cycle. A value of 5 ng ml^{-1} was used as the upper limit of normal. A CEA surge was defined as a 20% increase from baseline CEA followed by a 20% drop in subsequent CEA levels compared with the baseline without any change in chemotherapy drugs, schedule or dose (Sorbye & Dahl 2004). Clinical response was assessed every 6–8 weeks by radiological examination (computed tomography or magnetic resonance imaging). The response evaluation criteria in solid tumours (RECIST) was adopted for evaluation, and objective tumour response was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) (Therasse et al. 2000). Time to progression (TTP) was computed as the time interval between the start of the treatment and the date of disease progression, death or the last date the patient was known to be free of disease progression.

Statistical analysis

Statistical analysis was performed using SPSS software version 12. The differences between 'CEA surge' and 'non-CEA surge' groups on demographics and clinicopathologies were compared using χ^2 tests and Fisher's exact test.

Results

Patients

Medical records of 132 patients were screened. Thirty-three patients were not eligible due to normal CEA concentration (<5 ng ml^{-1}) (23 patients), no serial detection of CEA concentration throughout the treatment (six patients) or no evaluable metastatic disease (four patients). The remaining 99 patients who met the inclusion criteria were further analysed. Demographic and clinicopathological characteristics of the 99 patients are shown in Table 1.

Efficacy

All the patients received first- or second-line irinotecan-based combination chemotherapy. The FOLFIRI regimen (irinotecan plus LV and 5-Fu) was used as a first-line treatment in 30.3% (n=30), and as second-line treatment in 46.5% (n=46) of the cases. The XELIRI regimen (irinotecan plus capecitabine) was used as a first-line treatment in 17.2% (n=17), and as a second-line treatment in 6.1% (n=6) of the cases. Responses for the first-line chemotherapy regimen (including FOLFIRI and XELIRI) were PR 31.9% (n=15), SD 53.2% (n=25) and PD 14.9% (n=7). The median TTP was 6.5 months. Responses for the second-line chemotherapy regimen (including FOLFIRI and XELIRI) were PR 23.1% (n=12), SD 44.2% (n=23) and PD 32.7% (n=17). The median TTP was 5.1 months.

CEA surge

A CEA surge was seen in 11.1% (n = 11) of the patients. Among the cases that showed a CEA surge, the median baseline CEA level was 86 ng ml^{-1} (9–2740), and the median surge peak level was 129 ng ml^{-1} (17–4044) with an median increase rate of 73% (range 34–862%). The lowest

CEA measurement after the CEA peak was between 3 and 121 ng ml^{-1}. A CEA surge occurred at a median of 2 weeks (2–4 weeks) from the start of chemotherapy and lasted for 8–12 weeks. None of the 11 patients showed PD according to the RECIST criteria (four had a partial responses and seven had stable disease) (Table 2).

Table 1. Patient characteristics.

Variable	Frequency (%)
Age (years), median (range)	52 (25–76)
Gender	
M	60 (60.6)
F	39 (39.4)
KPS	
100	1 (1.0)
90	75 (75.8)
80	23 (23.2)
Baseline CEA (ng ml^{-1}), median (range)	26.1 (5.19–3942)
Primary tumour site	
Colon	60 (60.6)
Rectum	39 (39.4)
Histopathology	
Adenocarcinoma	81 (81.8)
Mucinous adenocarcinoma	18 (18.2)
Tumour grade	
Well	24 (24.2)
Moderate	59 (59.6)
Poor	4 (4.0)
Unknown	12 (12.1)
Chemotherapy	
FOLFIRI	76 (76.8)
XELIRI	23 (23.2)
Metastatic sites	
Liver	63 (63.6)
Lung	32 (32.3)
Peritoneum	27 (27.3)
No. of chemotherapy lines	
1st line	47 (47.5)
2nd line	52 (52.5)

KPS, Karnofsky Performance Status scale; CEA, carcinoembryonic antigen.

Comparison of 'CEA surge' and the 'non-CEA surge' patients

Demographic and clinicopathological characteristics including age, sex, KPS score, prechemotherapy lactate dehydrogenase (LDH) concentration, location of primary tumour, metastatic sites, histopathological subtype, tumour grade and chemotherapy regimen were compared between the 'CEA surge' and the 'non-CEA surge' groups. There were no differences between the 'CEA surge' group and the 'non-CEA surge' group in all the above factors (Table 3).

Discussion

CEA is a member of the immunoglobulin superfamily with a molecular mass of 180–200 kDa. It is a cell surface glycoprotein existing in normal colorectal epithelium and embryonic tissues. The antigen functions as a homotypic, intercellular adhesion molecule and seems to promote aggregation of colorectal carcinoma cells (Benchimol et al. 1989). CEA is the most commonly used tumour marker for colorectal cancer. Serum CEA concentration is less than 5 ng ml^{-1} in more than 95% of the healthy adults. However, up to 80% of colorectal cancer patients have an increased CEA level depending on the stage of the disease (Fletcher 1986). During the past decade, several studies have suggested that the serum CEA level variation could be used in monitoring chemotherapy (Hanke et al. 2001, Wang et al. 2002, Trillet-Lenoir et al. 2004). ASCO Guidelines for the 'Use of Tumor Markers in Gastrointestinal Cancer' also recommends CEA as a tumour marker for colorectal cancer in staging, treatment planning, postoperative surveillance and MCRC monitoring during systemic therapy (Locker et al. 2006). In general, an increase in CEA during treatment indicates disease progression. However, two studies, one by Sorbye and Dahl (2004) and another by Ailawadhi et al. (2006), reported a transient increase

Table 2. Characteristics of 'carcinoembryonic antigen (CEA) surge' and the association with clinical outcome.

Patient	CEA (ng ml^{-1})			Duration of surge (weeks)	Chemotherapy regimen	Chemotherapy line	Radiagraphic response	TTP (months)
	Baseline	Peak	Valley					
1	9	17	3	4	FOLFIRI	1st	PR	5
2	14	34	3	6	FOLFIRI	2nd	SD	6.7
3	18	28	12	8	FOLFIRI	2nd	PR	NPD at 5.7 m
4	20	33	5	10	FOLFIRI	1st	SD	9.3
5	24	94	9	8	FOLFIRI	1st	SD	7.8
6	86	129	24	9	XELIRI	2nd	SD	NPD at12.5 m
7	105	347	4	8	FOLFIRI	1st	SD	NPD at 6.6 m
8	115	155	73	9	XELIRI	1st	SD	NPD at 11.8 m
9	151	1453	3	6	FOLFIRI	1st	SD	11.5
10	155	267	41	6	FOLFIRI	2nd	PR	6.9
11	2740	4044	121	6	XELIRI	1st	PR	7.2

TTP, time to progress; PR, partial response; SD, stable disease; NPD, no progressive disease.

Table 3. Demographic and clinicopathological characteristics for patients with and without 'carcinoembryonic antigen (CEA) surge'.

Variable	Non-CEA surge patients *n* (%)	CEA surge patients *n* (%)	*p*-Value
n	88	11	
Age			
≤60 years	68 (77.3)	10 (90.9)	0.449
>60 years	20 (22.7)	1(9.1)	
Gender			
Male	54 (61.4)	6 (54.5)	0.748
Female	34 (38.6)	5 (45.5)	
KPS			
100	1 (1.1)	0 (0)	0.852
90	66 (75.0)	9 (81.8)	
80	21 (23.9)	2 (18.2)	
Baseline LDH (U l^{-1})			0.498
≤245 U l^{-1}	59 (67.0)	8 (72.7)	
>245 U l^{-1}	29 (33.0)	3 (27.3)	
Primary location			0.748
Colon	54 (61.4)	6 (54.5)	
Rectum	34 (38.6)	5 (45.5)	
Median metastatic number	1	1	1
Metastatic sites			
Liver	56 (63.6)	7 (63.6)	1
Lung	30 (34.1)	2 (18.2)	0.495
Peritoneum	23 (26.1)	4 (36.4)	0.485
Histopathology			
Adenocarcinoma	74 (84.1)	7 (63.6)	0.111
Mucinous adenocarcinoma	14 (15.9)	4 (36.4)	
Differentiation			
Well	23 (26.1)	1 (9.1)	0.501
Moderate	52 (59.1)	7 (63.6)	
Poor	3 (3.4)	1 (9.1)	
Unknown	10 (11.4)	2 (18.2)	
No. of chemotherapy lines			0.342
First-line	40 (45.5)	7 (63.6)	
Second-line	48 (54.5)	4 (36.4)	

KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase.

in CEA level despite objective response among patients receiving OXA combination chemotherapy for MCRC. Therefore, the 'ASCO 2006 update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer' has mentioned the possibility of a CEA surge between 4th and 6th week of a new therapy, especially after an OXA regimen.

Irinotecan is another effective cytotoxic drug which is commonly used for treating patients with advanced colorectal cancer. The ability of irinotecan to induce a CEA surge and its implications on clinical outcome have not been fully investigated. Sorbye and Dahl (2004) first described CEA surges in four out of a series of 27 patients who had received the FOLFOX regimen (LV, 5-Fu and OXA). Ailawadhi et al. (2006) reported CEA surges in 10 out of 89 patients and noted that nine out of 10 patients with CEA surges had received the FOLFOX regimen. Therefore they concluded that CEA surges might occur in patients receiving the FOLFOX regimen. However, only 18 patients in that study received the FOLFIRI regimen (first-line in 12 patients and second-line in six patients). Moreover, previous results from our institution (Li et al. 2009) revealed a transient CEA surge in three out of 49 MCRC patients treated with irinotecan-based combination chemotherapy. Therefore, we increased the number of patients in this study. As a result, we confirmed that a CEA surge could also be observed in patients receiving an irinotecan-based chemotherapy regimen. Among the 99 patients, 11 (11.1%) had a CEA surge. The percentage was somewhat lower than that in patients receiving the FOLFOX regimen (15% reported by Sorbye and Dahl (2004), and 16% reported by Ailawadhi et al. (2006)). The median increase rate of CEA surge was 73% (range 34–862%). The CEA surge occurred at a median of 2 weeks (2–4 weeks) from the start of chemotherapy and lasted for 8–12 weeks, which seemed to occur a little earlier and last a relatively shorter time than MCRC patients treated

with the FOLFOX regimen. However, like patients who received the FOLFOX regimen, none of the CEA surge patients who received irinotecan-based chemotherapy showed PD. To our knowledge, the present study is the first report to evaluate the CEA surge in MCRC patients treated with irinotecan combination chemotherapy.

The mechanism of the CEA surge is not fully understood. Certain chemotherapeutic agents seem to induce an increase in CEA expression. Many preclinical studies have confirmed that treatment of human colon cancer cell line with 5-Fu could increase the CEA expression either at the protein or transcript levels (Aquino et al. 1998, 2004). Prete et al. (2008) have reported that both 5-Fu plus LV or OXA alone could induce CEA expression in human colon cancer cell line HT-29, with a 4.7- or 2.7-fold increase, respectively, compared with the untreated controls. Ohtsukasa et al. (2003) exposed the human colon cancer cell line CoLo201 to 5-Fu, cisplatin (DDP) or (the active metabolite of irinotecan) SN-38 and found that 5-Fu dramatically increased the CEA mRNA expression at 50% inhibitory concentration (IC_{50}), while DDP and SN-38 induced higher expression of CEA mRNA only at IC_{80}. Further addition of DDP (at IC_{50}) to 5-Fu could increase CEA mRNA expression. However, they have not reported if SN-38 could act synergistically with 5-Fu to increase the CEA production. Furthermore, there are also some other non-cancer-related causes of elevated CEA, including gastritis, peptic ulcer disease, diverticulitis, chronic obstructive pulmonary disease, diabetes and any acute or chronic inflammatory state. CEA levels are also transiently affected by renal and hepatic diseases because of the involvement of these organs in the metabolism of such markers (Moertel et al. 1993). In the current series, all these conditions were excluded and therefore, this potential pitfall was avoided in the interpretation of CEA surge.

In conclusion, our study suggests that a CEA surge can be observed in MCRC patients receiving irinotecan-based chemotherapy. An early increase in CEA after irinotecan-based chemotherapy does not usually indicate progression of disease and failure of therapy, and should not lead to change of chemotherapy. Future guidelines might mention the possibility of a CEA surge not only in OXA-based chemotherapy, but also in irinotecan-based chemotherapy.

Acknowledgement

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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