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# Transient CEA Increase at Start of Oxaliplatin Combination Therapy for Metastatic Colorectal Cancer

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In general a rising carcinoembryonic antigen (CEA) level means tumor progression. We observed a transient increase in CEA level despite objective response among patients receiving chemotherapy for metastatic colorectal cancer. This surge phenomenon has not previously been described for patients with metastatic colorectal disease. CEA was measured every second week in 27 patients receiving oxaliplatin, 5-fluororuracil, and folinic acid as first-line therapy against metastatic colorectal cancer. Four patients (15%, 95% CI 5–31%) met the criteria for therapy-induced CEA surge. The time of reaching maximum CEA level varied from 13 to 56 days. Median rise in CEA from baseline was 263% (range 24–632%). An initial rise of CEA during chemotherapy in colorectal cancer patients may therefore not always indicate progression of disease but may be a transient CEA surge in patients responding to chemotherapy.

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Thirty years after its initial detection in serum, CEA is one of the most widely used tumor markers worldwide and certainly the most frequent marker used in colorectal cancer. Practice guidelines for tumor markers vary in some aspects (1). The 2000 update of the American Society for Clinical Oncology (ASCO) recommendations for the use of CEA in monitoring therapy in patients with advanced colorectal cancer state that the present data are insufficient to recommend routine use of serum CEA alone for monitoring response to treatment (2). However, they recommend CEA measurements at the start of treatment for metastatic disease and every 2 to 3 months during active treatment. Two values above baseline are considered adequate to document progressive disease even in the absence of corroborating radiographs. The benefit of CEA in monitoring chemotherapy treatment in metastatic colorectal cancer is still being debated (3–5).

Chemotherapy for advanced colorectal cancer has traditionally been 5-FU combined with folinic acid (FA), generally giving a response rate of about 15–20%, rarely above 30% (6). With the introduction of oxaliplatin and irinotecan response rates in the range 40–50% have regularly been reported (7, 8). Modulated 5-FU bolus regimens have until the year 2000 been the reference treatment in the US and in the Nordic countries. The Nordic FLv regimen consists of a short (3 min) bolus injection of 500 mg/m$^2$ 5-FU followed by a bolus injection of 60 mg/m$^2$ FA 30 min later (9, 10). In a compassionate use study we added oxaliplatin to our current Nordic 5-FU leucovorin schedule (Nordic FLOX) (11). As this was an experimental study we included repeated CEA measurements in this series.

The most common pattern of marker response during successful therapy is an exponential regression to normal levels. In a pilot patient treated outside this series, we observed a rise in CEA level despite normalization of liver function tests and a radiological verified tumor response. A surge of tumor markers in patients responding to chemotherapy has been described in other tumor groups. Non-seminomatous germ tumor cells (NSGCT) may produce alpha-feto-protein (AFP) and β-human chorionic gonadotropin (β-HCG). During initial weeks of treatment a transient increase of either one or both markers in serum is seen in 40–70% of the NSGCT patients (12, 13). In breast cancer patients responding to chemotherapy, a surge of CEA followed by a steady decline has been seen in 11–48% of patients (14–17). Loprinzi et al. found a CEA surge in 14 of 29 responding patients, with a mean rise of 243% of pretreatment CEA value (17). Peak CEA levels were seen 27 to 135 days after initiation of treatment. In six of these patients the initial CEA surge was incorrectly interpreted as

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evidence of disease progression and inappropriate therapy changes were made.

Based on the observation in our pilot patient, we therefore re-examined the laboratory CEA data for all 27 consecutive patients included in the study. A surge phenomenon was found in four patients. The relevance of this observation for the ASCO guidelines has recently been published as a letter to the editor (18). In this paper further results on the first observation of a surge phenomenon in colorectal cancer patients are presented.

## MATERIAL AND METHODS

A series of 27 patients received standardized chemotherapy as first-line treatment of radiological or histological confirmed metastatic disease from adenocarcinomas of the colon and rectum. The patients received oxaliplatin 85 mg/m$^2$ as a 2-hour infusion on day 1, followed by a 3-min bolus infusion with 5-fluorouracil (5-FU) 500 mg/m$^2$ and 30 min later a bolus infusion with folinic acid (FA) 60 mg/m$^2$. 5-FU and FA were given on days 1 and 2. The cycle was repeated every second week. Measurable lesions were reassessed by abdominal CT scan and chest x-ray after every fourth cycle, and response graded according to WHO criteria. Oxaliplatin was generously provided by Sanofi Winthrop. The regimen was very active as we recorded a 65% confirmed response rate and progressive disease in only one patient as best response (11). CEA was analyzed in all patients at baseline and before each cycle of chemotherapy. Serum CEA was analyzed in house by a microparticle enzyme immunoassay (MEIA) on an IMx (Abbott Laboratories, Abbott Park, IL, USA). Normal reference interval $<3.0$ μg/l.

The definition of CEA progression varies from a more than 10% rise from baseline value to a 20% and 50% increase of CEA (4, 16, 19). A 20% decrease in CEA concentration has been considered as a response to treatment, whereas others have defined biochemical responders as $>50\%$ drop in CEA level for more than 4 weeks (4, 20). We chose to define a CEA surge as more than 20% increase from basic value followed by a subsequent drop below 20% of the initial baseline value. Additional criteria were no progression of tumor lesions documented by radiological examination during the surge of CEA and the baseline CEA value taken less than 2 weeks before start of therapy.

## RESULTS

Four patients (15%, 95% CI 5–31%) met the criteria for therapy-induced CEA rise to more than 20% of the initial value followed by decline. Median rise of CEA from baseline was 263% (range 24–632%). Characteristics of the four CEA surge patients are given in Table 1. The initial case who stimulated this study did not meet the criteria (baseline CEA was taken 4 weeks before start of therapy) and is not included in this series. Baseline CEA was taken 1 day before first treatment in all four surge patients. The immediate rise in CEA was not related to tumor progression as 3 patients had a partial response and 1 had stable disease (slight regression). The kinetics of CEA changes are shown in Fig. 1.

## DISCUSSION

According to present recommendations, CEA is used to monitor response in colorectal cancer patients receiving chemotherapy. In responding patients the most common pattern of tumor marker response is regression towards normal levels (3, 17). A consistent rise in CEA is generally thought to be indicative of disease progression and some

**Table 1**

*Characteristics of the four CEA surge patients*

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age | 68 | 42 | 42 | 73 |
| Sex | F | F | M | F |
| No of metastatic sites | 2 | 1 | 4 | 2 |
| Best response | PR | PR | SD | PR |
| Time to progression (months) | 6.5 | 11.2 | 8.3 | 14.5 |
| Overall survival (months) | 8.2 | 27.3 | 8.4 | 35+ |
| Time to CEA peak (days) | 33 | 56 | 13 | 14 |
| Baseline CEA | 151 | 78 | 854 | 1800 |
| Peak CEA | 1106 | 252 | 3440 | 2229 |
| Lowest CEA after peak | 89 | 6 | 54 | 17 |
| Baseline LDH | 835 | 1179 | 3178 | 594 |
| LDH at CEA peak | 501 | 569 | 1799 | 357 |
| Baseline ALP | 542 | 723 | 2338 | 508 |
| ALP at CEA peak | 616 | 303 | 1447 | 380 |
| Baseline ALT | 74 | 461 | 227 | 20 |
| ALT at CEA peak | 121 | 142 | 125 | 27 |

LDH = lactate dehydrogenase (U/L), ALP = alkaline phosphatase (U/L), ALT = transaminase SGPT (U/L).

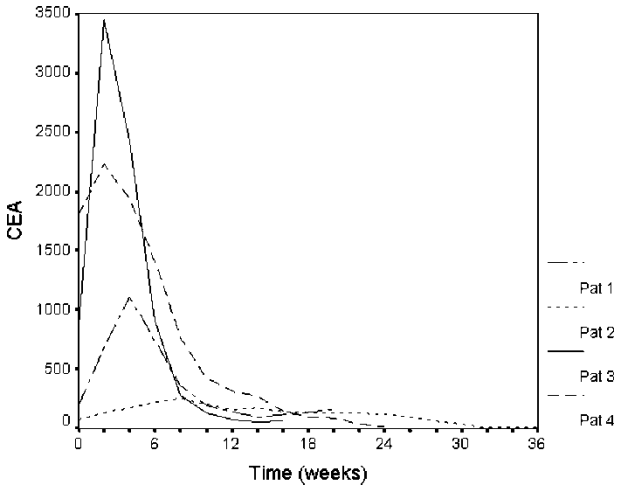


*Fig. 1.* CEA surge in patients with metastatic colorectal cancer responding to FLOX chemotherapy.

state that a rising tumor marker invariably heralds progressive disease (21). In a recent study the sensitivity of change in CEA level was 72% and 81%, respectively, in prediction of true responders and progressive diseases (4). A surge phenomenon has not previously been described for colorectal cancer patients responding to chemotherapy. In this study we found a clinically relevant CEA surge in 4 of 27 patients on therapy. We believe this new observation may be due to the introduction of a more effective chemotherapy regimen for metastatic colorectal cancer, inducing a larger tumor cell lysis then previous therapy. Oxaliplatin- and irinotecan-based chemotherapy is more effective as response rate is doubled compared with 5-FU regimens alone (7, 8). A Nordic multicentre study recently confirmed the high response rates of the present FLOX regimen (22).

A surge was seen in 15% of the patients receiving the FLOX regimen when CEA measurements were done at the start of a new treatment cycle, usually 2 weeks after the last chemotherapy treatment. CEA values in between this period are not known, but since the $t_{½}$ for CEA is about 5 days one would expect that the true number of responding patients with an undiscovered transient CEA surge is higher. A surge phenomenon has been seen in 40–70% of non-seminomatous testicular cancer patients and in 11–48% of responding breast cancer patients (12–17). The initial surge seen in treatment of testicular and breast cancer patients is also thought to be due to rapid tumor cell lysis in treatment responders. One could also speculate on other causes for a transient CEA increase. Among 99 patients who developed liver toxicity while on 5-fluororuracil based therapy, 19 had a false-positive transient CEA increase in the absence of disease progression (23). The CEA increase ranged from 5.1 to 34 μg/L. Most of these patients had elevation of alkaline phosphatase and transaminase. The four patients from our study did not show signs of liver toxicity, but rather a normalization of liver enzymes. Furthermore, CEA levels where much higher among our patients. The CEA surge in the 4 patients is therefore not likely to be due to liver toxicity. It has been shown that 5-FU increases CEA expression and shedding in colon cancer cells (24). The increased CEA shedding could potentially result in augmented circulating CEA in cancer patients subjected to 5-FU therapy. AFP surge after initiation of chemotherapy for NSGCT had, in a recent publication, an adverse prognostic significance, and the authors speculate as to whether AFP shedding by partly chemoresistant AFP-producing tumor cells could cause the surge rather than tumor cell lysis (25).

The possibility of a surge response must be taken into account when defining tumor marker guidelines. An early rise in tumor markers after treatment start should be serially followed to differentiate a true from a false rise. Our findings raise concern about the ASCO recommendation that two CEA values above baseline are adequate to document progressive disease even in the absence of corroborating radiographs (2). If we had followed this ASCO guideline and, as ASCO recommends, undertaken measurement of CEA every second month, patient number 2 would have been incorrectly interpreted as a treatment failure and FLOX therapy stopped. The patient would have been incorrectly removed from treatment giving her a time to progression of 11.2 months and a 27.3 month survival. To avoid inappropriate therapy changes based on clinical misinterpretation of a CEA surge as impending disease progression, we have suggested that future ASCO guidelines should mention the possibility of CEA surge. Furthermore no therapy changes should be based on CEA levels alone at all during the first 6 months of therapy (18).

When using tumor markers as part of monitoring in any kind of chemotherapy treatment for cancer patients, the possibility of a tumor marker surge must be kept in mind, avoiding misinterpreting the surge phenomenon as tumor progression. This will be especially important if a new more effective treatment with high response rates or rapid tumor destruction is introduced.

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