

## Scoring of Prognostic Parameters in Patients with Unresectable Advanced or Recurrent Colorectal Cancer Undergoing Chemotherapy

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### ABSTRACT

**Background** Suitable chemotherapy is needed to prolong the survival of patients with unresectable advanced or recurrent colorectal cancer. We scored the periodical changes of several prognostic markers during chemotherapy in patients with this type of cancer to discern the effectiveness of chemotherapy.

**Methods** Twenty consecutive patients with unresectable advanced or recurrent colorectal cancer were enrolled. All patients underwent combination chemotherapy with oxaliplatin or irinotecan plus 5-fluorouracil/leucovorin. Neutrophil/lymphocyte ratio (NLR), serum C-reactive protein (CRP), serum carcinoembryonic antigen (CEA) and serum albumin (ALB) were compared between the two periods (before chemotherapy and 3 months after it was started) in each patient. The scoring system was as follows: points are added when a patient shows a decrease of NLR, CRP and CEA and an increase of ALB at 3 months after the start of chemotherapy with a possible final score of +4. On the other hand, points are reduced if a patient shows an elevation of NLR, CRP and CEA and a decrease of ALB at 3 months after the start of chemotherapy with a possible final score of –4.

**Results** At 3 months after the start of first line chemotherapy, 13 patients showed positive scores but 7 patients showed zero or minus scores. According to our scoring system, we found the mean survival time (MST) of the 13 patients with plus scores was 34 months and this was significantly better than that of the 7 patients who showed zero or minus scores ( $P = 0.0008$ ).

**Conclusion** Our new scoring system is useful but when we find that first line chemotherapy is ineffective, we need to change it to second line chemotherapy as soon as possible. That may be the best treatment for patients with unresectable advanced or recurrent colorectal cancer.

**Key words** chemotherapy; colorectal cancer; inflammation; immunity; nutrition

5-Fluorouracil (5-FU) in combination with leucovorin (LV) (5-FU/LV) has been the standard systemic regimen for the treatment of unresectable advanced or recurrent colorectal cancer in most countries.<sup>1</sup> Recently, combination chemotherapies with oxaliplatin plus 5-FU/LV (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) have shown superior survival benefits when compared with 5-FU/LV, and led to a steady improvement in the median overall survival of these patients.<sup>2</sup> Also, a molecular target drug administered as a first-line treatment showed efficacy, and these therapies are considered as the standard treatment.<sup>3</sup> However, irrespective of the progress in chemotherapeutic drugs, the median overall survival was about 2 years in several pivotal phase III studies of chemotherapy for unresectable or metastatic colorectal cancer.<sup>4</sup> In order to improve the survival of these patients, it is important to decide the effectiveness of first line chemotherapy.

Several prognostic markers for patients with gastrointestinal carcinomas have been used for evaluating patients' response to chemotherapy. Neutrophil/lymphocyte ratio (NLR) of peripheral blood was detected as an immunological marker.<sup>5</sup> Serum albumin (ALB) level and C-reactive protein (CRP) have been recognized as the prognostic nutritional marker and marker of inflammation, respectively.<sup>6, 7</sup> Also, serum carcinoembryonic antigen (CEA) level was a good indicator for progression of colorectal cancer.<sup>8</sup> In the present study, we compared the periodical changes of these four markers (NLR, CRP, ALB and CEA) between the point before chemotherapy and at 3 months after the start of first line chemotherapy in consecutive patients with unresectable advanced or recurrent colorectal cancer. We scored increases or decreases of these markers and investigated whether or not these scores expressed reactivity of patients to anti-cancer chemotherapy.

### SUBJECTS AND METHODS

#### Patients

Between April 2008 and June 2009, 20 patients were diagnosed with unresectable advanced or recurrent

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Abbreviations: 5-FU, 5-fluorouracil; ALB, albumin; CEA, carcinoembryonic antigen; CRP, C-reactive protein; FOLFIRI, irinotecan plus 5-FU/LV; FOLFOX, oxaliplatin plus 5-FU/LV; LV, leucovorin; MST, mean survival time; NLR, neutrophil/lymphocyte ratio

**Table 1. Patients' characteristics**

|                             | Patients         |      |
|-----------------------------|------------------|------|
| Number                      | 20               |      |
| Age, mean (SD), yr          | 70.5 (7.9)       |      |
| Male/female                 | 13/7             |      |
| ECOG: PS 0/1                | 9/11             |      |
| Tumor: primary/recurrent    | 9/11             |      |
| Primary tumor: colon/rectum | 13/7             |      |
| Site of metastasis          | Liver            | 9    |
|                             | Lung             | 4    |
|                             | Peritoneum       | 5    |
|                             | Lymph node       | 2    |
| First line chemotherapy     | FOLFOX/FOLFIRI   | 15/5 |
|                             | Bevacizumab plus | 12   |

ECOG: PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, irinotecan plus 5-fluorouracil/ leucovorin; FOLFOX, oxaliplatin plus 5-5-fluorouracil/leucovorin.

colorectal cancer and were scheduled to undergo FOLFOX or FOLFIRI chemotherapy in our hospital. The Eastern Cooperative Oncology Group performance status of these patients was 0 or 1, and they had adequate bone marrow (platelet count > 100,000/L, white blood cell count > 4000/L, granulocyte count > 1500/L, haemoglobin > 10.0 mg/dL), renal (serum creatinine < 2.0 mg/dL), and hepatic (serum bilirubin < 2.0 mg/dL) functions. Fifteen patients underwent FOLFOX treatment, but 5 patients wanted FOLFIRI treatment instead. Bevacizumab was administered to 12 patients (FOLFOX, 9 patients and FOLFIRI, 3 patients). The Ethics Committee of Tottori University (approval number 1223) approved this study in 2008. Informed consent was obtained from all 20 patients. They were followed up until April 2013 and their details are shown in Table 1.

### Blood samples

Blood samples were taken from each patient before start of the first line chemotherapy and at 3 months after the start of chemotherapy. NLR, serum ALB, CRP and CEA levels were compared between the two periods.

### Scoring system

At 3 months after the start of chemotherapy, the NLR, CRP, CEA and ALB levels were compared with those of before chemotherapy in each patient. Scoring was as follows: decreased NLR, +1; increased NLR, -1; decreased CRP, +1; increased CRP, -1; decreased CEA, +1; increased CEA, -1; increased ALB, +1; decreased ALB, -1. In cases with a decrease of NLR, CRP and CEA and with an elevation of ALB at 3 months after the start of chemotherapy, we gave a score of +4. On the other hand, when we found cases with an elevation of

NLR, CRP and CEA and with a decrease of ALB at 3 months after the start of chemotherapy, we gave a -4. If the patient showed a decrease of NLR and CRP, and an increase of CEA and ALB at 3 months after the start of chemotherapy, his final score was +2. A "0 score" was given when we found equal levels of NLR, CRP, CEA and ALB before and after chemotherapy.

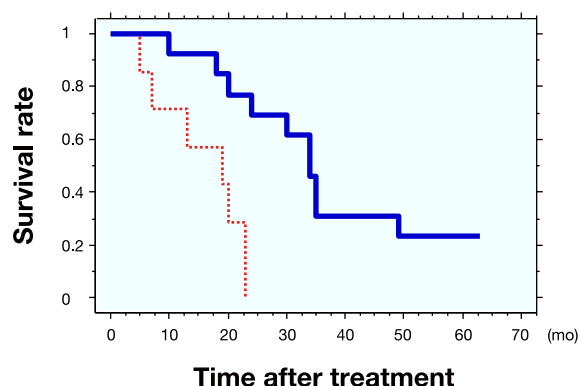
### Statistics

The chi-square test for independence, Fisher's exact probability test, and the Mann-Whitney *U* test were used to compare the differences between the two parameters. Spearman's rank correlation coefficient was used to assess the correlation between the two parameters. Survival rates of the two groups were estimated by the Kaplan-Meier method, and the statistical differences between survival curves were examined by the log-rank test. A *P* value of < 0.05 was regarded as statistically significant.

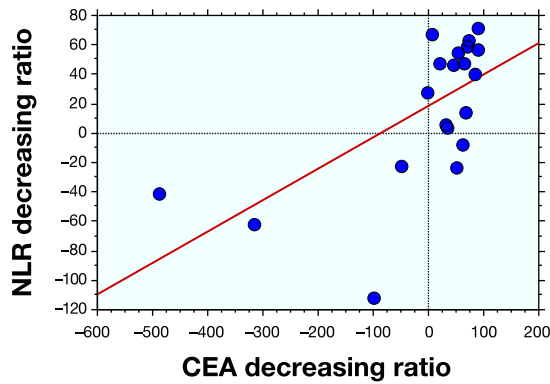
### RESULTS

All patients were followed up at our hospital. The median follow-up period of the 20 patients was 28.3 months (range, 5–63 months). During the follow-up period, 17 patients died due to disease progression. The mean pre-treatment levels of NLR, CRP, CEA and ALB were 2.7, 1.1 mg/dL, 237.7 ng/mL and 3.8 g/dL. And the mean post-treatment levels were 2.0, 0.9 mg/dL, 153.6 ng/mL and 3.7 g/dL each. At 3 months after the start of first line chemotherapy, decreased NLR was detected in 14, decreased CRP was detected in 15, decreased CEA was detected in 15, and increased ALB was detected in 8 patients.

According to our scoring system, we found that 6 were +4, 2 were +3, 3 were +2 and 2 patients were +1. However, 3 were 0 and 4 patients were -4 and -3. The mean survival time (MST) of 13 patients with plus



**Fig. 1.** The survival curve of 13 patients with plus scores (solid line) is significantly better than that of 7 patients with minus or zero scores (dotted line). The difference is statistically significant ( $P = 0.0008$ ).



**Fig. 2.** There is a significantly positive correlation between CEA decreasing ratios (X axis) and NLR decreasing ratios (Y axis,  $\rho = 0.651$ ,  $P = 0.0046$ ). CEA, carcinoembryonic antigen; NLR, neutrophil/lymphocyte ratio.

scores was 34 months and this was significantly better than that of the 7 patients who showed zero or minus (19 months, Fig. 1,  $P = 0.0008$ ).

We calculated the decrease ratio [(pre – post)/pre × 100%] of NLR, CRP and CEA in each case and calculated the increase ratio [(post – pre)/pre × 100%] of ALB in each case. We found strong correlations among these ratios [NLR and CRP:  $\rho = 0.615$ ,  $P = 0.0073$ ; NLR and CEA:  $\rho = 0.651$ ,  $P = 0.0046$  (Fig. 2); NLR and ALB:  $\rho = 0.59$ ,  $P = 0.0102$ ; CRP and CEA:  $\rho = 0.497$ ,  $P = 0.0303$ ; CRP and ALB:  $\rho = 0.614$ ,  $P = 0.0075$  and CEA and ALB:  $\rho = 0.483$ ,  $P = 0.0354$ ].

We investigated the prognostic strength of each parameter. Then, we divided the patients into two subgroups according to the median levels of each parameter. Table 2 shows that the CEA decrease ratio was a good parameter of prognosis of patients with unresectable advanced or recurrent colorectal cancer undergoing chemotherapy.

**DISCUSSION**

For patients with unresectable advanced or recurrent colorectal cancer, it is important to continue effective chemotherapy for as long as possible. FOLFOX or FOLFOX plus bevacizumab has been recognized as a good first line chemotherapy for these patients,<sup>9</sup> but in cases where first line chemotherapy is ineffective, we should change the treatment to second line chemotherapy as soon as possible. To find out whether first line chemotherapy is effective or not, we looked for suitable markers. Another point is that several parameters have been reported as useful markers to determine the effectiveness of chemotherapeutic drugs in advanced colorectal cancer.<sup>10, 11, 12</sup> But when we use these markers, we need to do special immunostaining of resected

specimens or bioptic samples, or we need to check the periodical changes of tumors by using an imaging analyzer. These methods may be useful, but it will take lots of time and money and/or require special techniques to perform these methods.

It is well known that circulating lymphocytes play an important immunological role in various carcinomas.<sup>13, 14</sup> In addition, a strong correlation between cancer progression and lymphopaenia was detected in patients with clear cell renal carcinoma.<sup>14, 15</sup> Lissoni et al. reported that independently of tumor histotype and chemotherapeutic regimen, lymphocytosis occurred in patients who achieved an objective tumor regression in response to chemotherapy, and the mean lymphocyte count observed at the end of the chemotherapeutic treatment was significantly higher than that seen before the onset of treatment.<sup>16</sup> They added that the mean lymphocyte count decreased with chemotherapy in patients with tumor progression. Based on this finding, we invented a new scoring system using NLR, CRP, CEA and ALB to decide the effectiveness of first line chemotherapy. This system is very simple and we can use this system without special techniques.

Even though the total number of our investigated cases was small, we found that this scoring system accurately predicted the prognosis of patients with unresectable advanced or recurrent colorectal cancer during chemotherapy in our study. Specifically, CEA should be a good indicator of tumor progression, but many colorectal tumors that did not express CEA elevation according to the tumor progression have been reported.<sup>17, 18</sup> In such cases, peripheral lymphocytes counts, CRP and serum ALB should be good indicators. In this paper, we discuss the usefulness of a scoring system as a parameter

**Table 2. Prognostic analysis of 20 patients**

|                    | Median (%) | n  | MST (mo) | P      |
|--------------------|------------|----|----------|--------|
| NLR decrease ratio | High       | 10 | 34       | 0.3069 |
|                    | Low        | 10 | 19       |        |
| CRP decrease ratio | High       | 10 | 24       | 0.9685 |
|                    | Low        | 10 | 20       |        |
| CEA decrease ratio | High       | 10 | 34       | 0.0119 |
|                    | Low        | 10 | 19       |        |
| ALB increase ratio | High       | 10 | 30       | 0.3873 |
|                    | Low        | 10 | 23       |        |

ALB, albumin; CEA, carcinoembryonic antigen; CRP, C-reactive protein; MST, mean survival time; NLR, neutrophil/lymphocyte ratio.

of effectiveness of first line chemotherapy for colorectal cancer. For all patients, peripheral blood samples were checked every month and these data are what our system used. NLR, serum ALB, CRP and CEA levels were compared between the two periods (before the start of first line chemotherapy and at 3 months after the start of chemotherapy). Usually, the response assessment has been checked every 2 or 3 months during chemotherapy in advanced colorectal cancers.<sup>19</sup> Our scoring system may indicate total patient conditions including immunological aspects of patients or tumor regression during chemotherapy. However, the prognostic differences among the patients who showed scores of +4, +3, +2, +1, 0, -1, -2, -3 and -4 were unclear. In order to clarify this, we need to investigate our scoring system with a larger scale study of colorectal cancer patients.

In conclusion, when we suspect that first line chemotherapy will be ineffective for patients, our scoring system can help us to decide to change to the second line chemotherapy as soon as possible. That may be the best treatment for patients with unresectable advanced or recurrent colorectal cancer undergoing chemotherapy.

*The authors declare no conflict of interest.*

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