SHORT COMMUNICATION

The impact of white blood cell count and hemoglobin level on the response to radiotherapy in patients with colorectal cancer

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KEYWORDS
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Abstract Radiotherapy (RT) plays a much more important role in the treatment of colorectal cancer when it can be used to reduce the size of a tumor prior to the local excision of the cancer. In order to find other factors possibly related to radiosensitivity, we evaluated the relationships between circulating blood cell counts and RT effects. In 81 cases of rectal cancer, we examined white blood cell and platelet counts, as well as hemoglobin (Hb) levels, prior to RT, and also investigated their associations with the treatment response rate and with other clinicopathological factors. The patients with anemia had significantly worse RT responses, whereas patients with high white blood cell counts (>7400/μL) showed better responses (p < 0.001). Cancer patients with low Hb levels do not respond as well to RT as nonanemic
Introduction

Colorectal cancer (CRC) was the third most commonly diagnosed cancer and the fourth most fatal cancer worldwide in 2008. Recent studies have shown that preoperative radiotherapy (RT) can lead to a reduction in tumor size in CRC. However, in unresponsive cases, RT may have disadvantages, such as delaying surgery or immunosuppression. Therefore, suitable selection of patients for preoperative RT is important for improving the outcomes of those with CRC.

Anemia is known to produce tumor hypoxia, which confers radioresistance through the hypoxia-associated reduction in free-radical production and consequent RT-induced DNA damage. Previous studies have shown that the survival rate at 5 years for patients with anemia was 22%. For nonanemic patients, however, the rate at 5 years was 36%, a significant increase compared with anemic patients ($p = 0.0016$).

Previous research has shown that radiosensitivity depends not only on the biological characteristics of tumor cells but also on the tumor microenvironment. In our study, we examined the laboratory data including white blood cell (WBC) counts, Hb levels, and platelet counts during RT and the post-RT period prior to the surgery, which may reflect systemic responses against tumor cells damaged by irradiation.

Materials and methods

Selection of patient samples

Eighty-one patients with CRC received RT in the Cancer Center at Kaohsiung Medical University Hospital from May 2005 to February 2009. Pre-RT blood cell counts as well as other clinical and pathological parameters were available in all 81 cases, therefore data from all 81 patients were included in this study.

Laboratory test results and other clinical data collection

A pre-RT complete blood count, including WBC counts, Hb levels, and platelet counts, was routinely determined in peripheral venous samples. Blood test results for each patient were obtained from the laboratory information system of the Kaohsiung Medical University Hospital. Detailed clinicopathologic information was obtained from the medical records system.

Tumor response

The assessment of pathological tumor response to preoperative RT was based on a standardized tumor regression grading (TRG), as described by Dworak et al. TRG was determined by the amount of viable tumor versus fibrosis, ranging from TRG 4 (no viable tumor cells detected) to TRG 0 (fibrosis completely absent). TRG 3 was defined as a regression of more than 50% with fibrosis outgrowing the tumor mass; TRG 2 was defined as a regression of less than 50%; and TRG 1 was basically defined as a morphologically unaltered tumor mass. In this study, pathological tumor response was defined as ranging between TRG 2 and TRG 4.

Statistical analysis

All statistical data were analyzed using the SPSS 18.0 software program (SPSS Inc., Chicago, IL, USA). A two-sided Pearson chi-square test was used to analyze the potential correlation between the RT response and the clinicopathological features of the study participants. A Student $t$ test was used to compare the distribution of pre-RT WBC counts and Hb level between RT response and nonresponse cases. A probability level of less than 0.05 was considered statistically significant.

Results

Clinicopathological features

Eighty-one CRC patients (50 men and 31 women) were included in this study. The median age of the patients was 63.5 (range 34–88) years at the date of diagnosis. After preoperative RT, 60 patients (70%) achieved a pathological tumor response. These patients’ characteristics and clinicopathological findings are listed in Table 1.

Relationship between WBC count, Hb level, and RT response

The correlation between preoperative RT WBC count, Hb level, and treatment response was analyzed. WBC counts were divided into four groups according to the criteria described by Shankar et al. When grouped by WBC count, patients with higher WBC counts ($\geq 7.4 \times 10^3/\mu$L) had better treatment responses than those with lower ones ($< 7.4 \times 10^3/\mu$L; $p < 0.001$), whereas those with higher Hb levels ($\geq 12$ g/dL) had better treatment responses than those with lower ones ($< 12$ g/dL; $p = 0.018$; Table 1).
Distribution of pre-RT WBC counts

Fig. 1 shows the distribution of pre-RT WBC counts and Hb level in responsive and nonresponsive patients, respectively. The mean WBC count was significantly greater among patients with an RT response than in nonresponse cases (8.0 ± 2.05 vs. 5.8 ± 1.87 × 10^3/µL; p < 0.001). The mean Hb level was significantly greater among patients with an RT response than in nonresponse cases (12.73 ± 2.05 vs. 11.46 ± 1.74 g/dL, p = 0.013).

Discussion

Adjuvant RT is considered the standard treatment for advanced CRC. Recent studies have suggested that there is an association between the radiosensitivity of the tumor microenvironment. Grigiene and colleagues found that the hemoglobin (Hb) level prior to the treatment was an independent prognostic factor for overall survival, disease-free survival, and local relapse-free survival for patients treated with irradiation. We hypothesized that WBC counts and Hb levels, which reflect patient conditions, may critically affect responsiveness to RT. In fact, our results show that WBC counts and Hb levels are indeed correlated with the RT responses.

Previous studies have suggested that clinical factors and some molecular markers such as the circumferential extent of the tumor, the treatment interval between radiation and surgical resection, and the levels of epidermal growth factor receptor, Ki-67, Bcl-2/Bax, and vascular endothelial growth factor—are significantly correlated with clinical response. In the future, we will try to combine these prognostic markers with WBC counts and Hb level in order to enhance the prediction to the RT responsiveness. Furthermore, to

Table 1 Clinical and pathological factors in 81 patients with colorectal cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonresponse (n = 21)</th>
<th>Response (n = 60)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.2 ± 14.0</td>
<td>63.9 ± 10.7</td>
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<tr>
<td>Sex</td>
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<td></td>
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<tr>
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</tr>
<tr>
<td>Female</td>
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<td>23</td>
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<td>TNM stage</td>
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<td></td>
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</tr>
<tr>
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<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>III</td>
<td>15</td>
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</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>WBC (10^3/µL)</td>
<td>&lt;5.3</td>
<td>9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>5.4–6.2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6.3–7.3</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>≥7.4</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
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</tr>
<tr>
<td></td>
<td>≥12.0</td>
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<td>43</td>
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<tr>
<td></td>
<td>&lt;12.0</td>
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<td>17</td>
</tr>
<tr>
<td>Platelet (10^5/µL)</td>
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<td>2</td>
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<td>1.5–4.0</td>
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<tr>
<td></td>
<td>&lt;1.5</td>
<td>2</td>
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</tbody>
</table>

*p < 0.05 represents a statistically significant difference using chi-square test.

TNM = tumor, node, metastasis staging system; WBC = white blood cell.

Figure 1 (A) Distribution of pre-RT WBC counts. The mean WBC count is significantly greater among patients with an RT response than in nonresponse cases (8.0 ± 2.05 vs. 5.8 ± 1.87 × 10^3/µL, p < 0.001). (B) Distribution of pre-radiotherapy Hb level. The mean Hb level was significantly greater among those patients with an RT response than in nonresponse cases (12.73 ± 2.05 vs. 11.46 ± 1.74 g/dL, p = 0.013). *p < 0.05 represents a statistically significant difference using the Student t test. Hb = hemoglobin; RT = radiotherapy; WBC = white blood cell.
understand the association between anemia and high radioresistance, we will also apply the mouse model for further investigation.

**Conclusion**

Our findings indicate that WBC counts and Hb levels have a significant impact on radiosensitivity in patients with CRC. In addition, a complete blood count is a routine examination, and so a given patient’s WBC count and possible anemia can be easily assessed. Further studies with larger sample sizes are needed to validate these findings.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**