Serum C-reactive protein predicts poor prognosis in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy

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ABSTRACT

Background

We aimed to evaluate the association of serum C-reactive protein (CRP) with prognosis in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy.

Methods

We retrospectively reviewed 79 patients with locoregionally advanced nasopharyngeal carcinoma (cT3–4N0–3M0) treated with chemoradiotherapy. Chemoradiotherapy consisted of external-beam radiotherapy to the nasopharynx (70–80 Gy), the lymph node–positive area (60–70 Gy), and the lymph node–negative area (50–60 Gy) combined with 3 cycles of various platinum-based regimens delivered at 3-week intervals. Elevated CRP was defined as more than 8 mg/L. The survival rate was calculated using the Kaplan–Meier method, and univariate and multivariate analyses (Cox proportional hazards model) were used to identify factors significantly associated with prognosis.

Results

During the median follow-up of 3.9 years (range: 1–5.5 years), 23 patients died from nasopharyngeal cancer. The 5-year cancer-specific survival (CSS) rate was 62.90%. Before chemoradiotherapy, 18 patients had high serum CRP; the CSS rate in that subgroup was significantly worse than the rate in the remaining patients (p = 0.0002). Multivariate analysis showed that CRP was an independent prognostic indicator of CSS, with a hazard ratio of 3.04 (95% confidence interval: 1.22 to 7.55; p = 0.017). Among the 18 patients with elevated serum CRP, 9 achieved normal serum CRP after chemoradiotherapy, of whom 5 remained living with no evidence of recurrence or metastasis during follow-up. By contrast, the remaining 9 patients in whom serum CRP did not normalize after chemoradiotherapy died within 4.2 years.

Conclusions

Elevated serum CRP before treatment predicts poor prognosis in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy.

KEY WORDS

Nasopharyngeal carcinoma, C-reactive protein, chemoradiotherapy, cancer-specific survival

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common form of head-and-neck cancer in China, and it is endemic in southern China. Radiation therapy is the initial mainstay approach to treating NPC. Early detection and intervention play a critical role in NPC prognosis, but most patients present with advanced disease and need a multidisciplinary approach. Concurrent chemoradiotherapy has long been considered the standard treatment for advanced NPC. Some studies have shown that concurrent administration of chemotherapy and radiotherapy is superior to sequential therapy or radiotherapy alone for achieving locoregional control. Chemoradiotherapy is therefore the standard regimen in the treatment of locoregionally advanced NPC. However, in some patients, the disease progresses within a few years after chemoradiotherapy. Identifying a prognostic factor for early progression would therefore allow for a better therapeutic approach to patients with locoregionally advanced NPC.

The presence of a systemic inflammatory response is increasingly being recognized as being associated with poor survival in various malignancies. The aim of the present study was to investigate the association of serum C-reactive protein (CRP) with prognosis in patients with locoregionally advanced NPC.
2. METHODS

We retrospectively reviewed patient records and identified 79 patients with locoregionally advanced NPC (Union for International Cancer Control stages T3–4N0–3M0) who had been treated with chemoradiotherapy between January 2007 and December 2012 at our institution. Serum CRP was defined as the value estimated at dawn before the start of chemoradiotherapy. That value was unavailable in 17 patients; 62 patients therefore constituted the study group. At diagnosis, none of the study patients had any inflammatory disease.

Serum CRP was measured using a CRP kit for the IMMAGE Immunochemistry System (Beckman Coulter, Brea, CA, U.S.A.). The cut-off value for abnormal elevation of serum CRP was set at 8 mg/L (0.8 mg/dL) as specified in the reagent manual. Patients with a serum CRP value exceeding 8 mg/L before chemoradiotherapy were assigned to the elevated CRP group. Within that group, we also identified patients who achieved a normal serum CRP value (<8 mg/L) within 1 month after chemoradiotherapy (“CRP responders”).

Associations between baseline characteristics and serum CRP were analyzed using the chi-square test. Cancer-specific survival (CSS) was calculated and analyzed using the Kaplan–Meier method and the log-rank test. Univariate and multivariate analyses used Cox proportional hazards models and incorporated factors determined before chemoradiotherapy, including age, sex, tumour stage, nodal status, histologic grade, chemotherapy regimen, performance status, and serum CRP. The duration of CSS was defined as the interval starting from the date of diagnosis with locoregionally advanced NPC. In all statistical tests, the significance level was set at $p < 0.05$.

Written informed consent was obtained from each patient before study start. The study was approved by our centre’s Ethics Committee and was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice.

3. RESULTS

Table 1 describes the clinical characteristics of the study patients. Chemoradiotherapy consisted of external-beam radiotherapy (50–80 Gy) with concurrent chemotherapy. Platinum-based regimens were used in 52 patients: fluorouracil and platinum were administered in 37 patients; 15 patients received carboplatin and paclitaxel. The other 10 patients received a combination of cisplatin or carboplatin with docetaxel.

Radiation doses to the nasopharynx, the lymph node–positive area, and the lymph node–negative area were 70–80 Gy, 60–70 Gy, and 50–60 Gy respectively, given in daily fractional doses of 1.8 Gy or 2 Gy 5 days per week. Chemotherapy was given systemically every 3 weeks for 9 weeks during radiotherapy; another cycle was given after the end of radiotherapy. All patients received 4 cycles of chemotherapy. In 4 patients (6%), the radiation dose was reduced because of acute oropharynx toxicity (median total dose: 50 Gy; range: 45.0–65.0 Gy).

During the median follow-up of 3.9 years (range: 1–5.5 years), 23 patients (37.10%) died of nasopharyngeal cancer. The 5-year CSS rate was 62.90% (Figure 1). We observed no differences in clinical characteristics between the patients with elevated and normal serum CRP, except for tumour histologic grade. In the 18 patients (29.03%) with an elevated serum CRP, histologic grade was significantly higher ($p = 0.028$, Table 1). Deaths from NPC numbered 13 in the elevated CRP group ($n = 18, 72.22\%$) and 10 in the normal CRP group ($n = 44, 22.73\%, p = 0.019$).

As Figure 2 shows, the CSS rate was significantly worse in the elevated CRP group than in the normal CRP group ($p = 0.0002$), with the 5-year CSS rates being 27.78% and 77.27% respectively. Of all clinical characteristics, N stage (high), histologic grade (high), and performance status (high) were associated with a poorer CSS rate (Table II, $p = 0.035, 0.042, and 0.047$ respectively). Univariate and multivariate analyses of clinical characteristics before chemoradiotherapy showed (Table II) that serum CRP was an independent prognostic indicator for CSS, with a hazard ratio of 3.04 (95% confidence interval: 1.22 to 7.55; $p = 0.017$).

In the group of patients with elevated CRP ($n = 18$), 9 patients registered normal serum CRP levels after chemoradiotherapy. In those 9 CRP responders, 5 remained living with no recurrence or metastasis during a median follow-up of 3.9 years (range: 1–5.5 years). By contrast, the remaining 9 patients who did not respond (no CRP normalization after chemoradiotherapy) died of their disease within 4.2 years because of locoregional recurrence or distant metastasis. Prognosis was worse in non-responding patients than in CRP responders ($p = 0.029$).

4. DISCUSSION

The presence of elevated serum CRP has been reported to be associated with a poor prognosis in patients with various malignancies, including laryngeal cancer, colorectal cancer, gastric cancer, and soft-tissue sarcoma$^{6–9}$. In the present study of the association of serum CRP with prognosis in patients with locoregionally advanced NPC treated with chemoradiotherapy, serum CRP before chemoradiotherapy predicted poor prognosis. That finding is consistent with reports that serum CRP is an independent unfavourable prognostic factor in patients with head-and-neck cancer$^{10,11}$. The presence of a systemic inflammatory response is reported to be associated with poor prognosis in patients with various malignancies. Recently, Liao et al.$^{12}$
reported that interleukin 6 was highly expressed in NPC tissues and that LPLUNCl can suppress interleukin 6–induced NPC cell proliferation. A member of the bactericidal permeability-increasing protein and lipid-binding protein family, LPLUNCl can be secreted by goblet cells and minor mucosal glands of the upper respiratory tract and oral cavity. The protein inhibits lipopolysaccharide-induced interleukin 6 expression in NPC cells and thus inhibits NPC cell proliferation, induces NPC cell arrest, and promotes NPC cell apoptosis. The correlation between elevated serum CRP and a poor prognosis might reflect the prognostic value of tumour-produced interleukin 6, an inducer of CRP production in the liver.

In the present study, it was interesting that, apart from being a prognostic indicator, serum CRP was a useful marker of the clinical course of patients with...
locoregionally advanced NPC treated with chemoradiotherapy. In the elevated CRP group, outcomes were more favourable in the CRP responders than in patients whose CRP level did not decline to a more normal level. Thus, a return to normal serum CRP might be able to act as a surrogate endpoint of clinical outcome. The failure of serum CRP to normalize after treatment indicated further disease progression and a need for adjuvant therapy. Our study included only patients with locoregionally advanced head-and-neck cancer who underwent chemoradiotherapy, and CRP could therefore be a practical adjunct in the stratification of patients with locoregionally advanced NPC both before and after treatment.

In assessing CRP elevation, the presence of other inflammatory disease should be considered, because CRP is a nonspecific inflammatory marker. However, measurements of serum CRP are simple and low-cost. Therefore, despite weak sensitivity, CRP could be routinely measured as a practical clinical marker in patients with locoregionally advanced NPC treated with chemoradiotherapy. Higher pre-treatment levels of serum CRP might also possibly identify candidates for more aggressive surveillance and individualized treatment. However, our study was an exploratory and retrospective effort; the results should be confirmed in an independent sample studied prospectively. Further studies are also needed to determine the biologic basis for the association, which might suggest new targets for innovative biologically-based adjuvant therapy in this challenging disease.

5. CONCLUSIONS

In the present study, we tested whether serum CRP was associated with prognosis in patients with locoregionally advanced NPC treated with chemoradiotherapy. Elevated serum CRP before treatment predicts poor prognosis in patients with locoregionally advanced NPC treated with chemoradiotherapy. Our results also indicated that change in serum CRP with treatment is an independent prognostic indicator in patients with locoregionally advanced NPC.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest and declare that we have none.

TABLE II Univariate and multivariate analysis of cancer-specific survival in patients treated with chemoradiotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>Patients</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥60 years vs. &lt;60 years</td>
<td>21/41</td>
<td>1.51 0.67 to 3.40 0.321</td>
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<tr>
<td>Sex</td>
<td>Men vs. women</td>
<td>44/18</td>
<td>1.64 0.61 to 4.39 0.326</td>
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<tr>
<td>T Stage</td>
<td>T3 vs. T4</td>
<td>42/20</td>
<td>1.28 0.56 to 2.92 0.560</td>
<td></td>
</tr>
<tr>
<td>N Stage</td>
<td>N0 vs. N1 vs. N2 vs. N3</td>
<td>7/24/21/10</td>
<td>1.63 1.04 to 2.57 0.035</td>
<td></td>
</tr>
<tr>
<td>Histologic grade</td>
<td>G1 vs. G2 vs. G3 vs. G4</td>
<td>12/18/22/10</td>
<td>1.56 1.02 to 2.38 0.042</td>
<td></td>
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<tr>
<td>Performance status</td>
<td>0 vs. 1 vs. 2</td>
<td>9/45/8</td>
<td>2.14 1.01 to 4.52 0.047</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>FP vs. CP vs. PD</td>
<td>21/19/17</td>
<td>1.34 0.81 to 2.22 0.250</td>
<td></td>
</tr>
<tr>
<td>Serum C-reactive protein</td>
<td>≤8 mg/L vs. &gt;8 mg/L</td>
<td>44/18</td>
<td>3.55 1.56 to 8.05 0.002</td>
<td>3.04 1.22 to 7.55 0.017</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; FP = fluorouracil and platinum; CP = carboplatin and paclitaxel; PD = cisplatin or carboplatin and docetaxel.
8. REFERENCES


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