Curr Oncol, Vol. 22, pp. 20-24; doi: http://dx.doi.org/10.3747/co.22.2178

ORIGINAL ARTICLE

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[1]. 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[2]. Some studies have shown that concurrent administration of chemotherapy and radiotherapy is superior to sequential therapy or radiotherapy alone for achieving locoregional control[2]. Chemoradiotherapy is therefore the standard regimen in the treatment of locoregionally advanced NPC[3]. 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[4,5]. 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 I 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 I). 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]

TABLE I Relationship between serum C-reactive protein and clinical characteristics of patients treated with chemoradiotherapy

Variable	*Serum C-reactive protein*		p *Value*
	Normal	*Elevated*	
Patients (*n*)	44	18	
Age (years)			
Mean	55	54	
Range	32–75	35–73	
Sex [*n* (%)]			
Men	30 (68.18)	14 (77.78)	
Women	14 (31.82)	4 (22.22)	0.450
T Stage [*n* (%)]			
T3	29 (65.91)	13 (72.22)	
T4	15 (34.09)	5 (27.78)	0.629
N Stage [*n* (%)]			
N0	6 (13.64)	1 (5.56)	
N1	21 (47.73)	3 (16.67)	
N2	12 (27.27)	9 (50.00)	
N3	5 (11.36)	5 (27.78)	0.110
Histologic grade [*n* (%)]			
Well differentiated (grade 1)	9 (20.45)	3 (16.67)	
Moderately differentiated (grade 2)	13 (29.55)	5 (27.78)	
Poorly differentiated (grade 3)	15 (34.09)	7 (38.89)	
Undifferentiated (grade 4)	7 (15.91)	3 (16.67)	0.028
Performance status [*n* (%)]			
0	7 (15.91)	2 (11.11)	
1	30 (68.18)	15 (83.33)	
2	7 (15.91)	1 (5.56)	0.268
Chemotherapy regimens [*n* (%)]			
Fluorouracil and platinum	28 (63.64)	9 (50.00)	
Carboplatin and paclitaxel	10 (22.73)	5 (27.78)	
Cisplatin or carboplatin and docetaxel	6(13.63)	4(22.22)	0.127
Complete response			
Yes	34 (77.27)	14 (77.78)	
No	10 (22.73)	4 (22.22)	0.966

reported that interleukin 6 was highly expressed in NPC tissues and that LPLUNC1 can suppress interleukin 6–induced NPC cell proliferation. A member of the bactericidal permeability-increasing protein and lipid-binding protein family, LPLUNC1 can be secreted by goblet cells and minor mucosal glands of the upper respiratory tract and oral cavity[13]. 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[12,13]. 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[14].

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

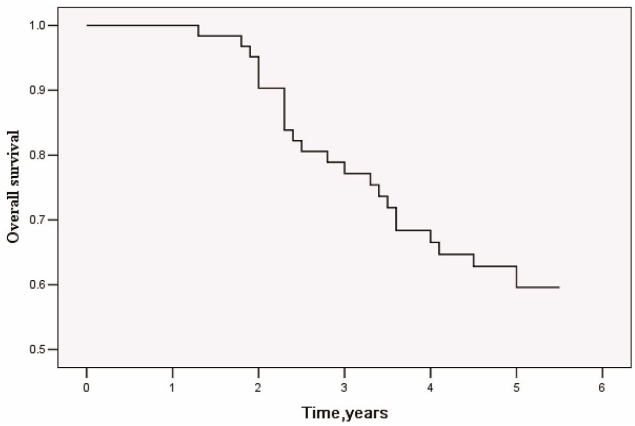

FIGURE 1 Overall survival for 62 patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy.

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[15–17]. 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 pretreatment 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.

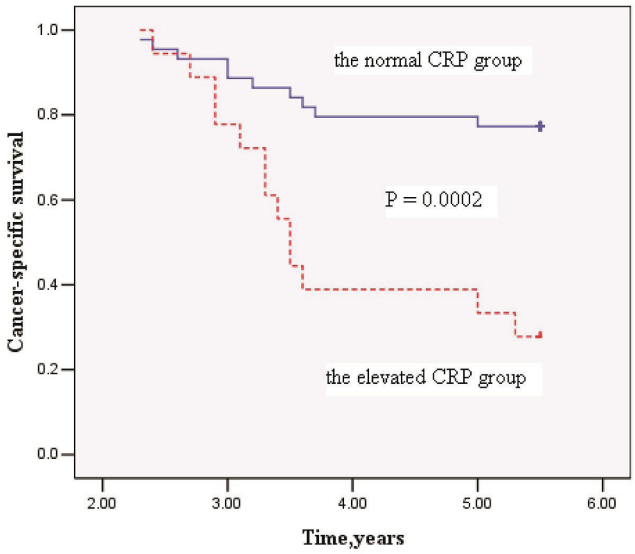

FIGURE 2 Cancer-specific survival by C-reactive protein group (normal or elevated).

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

Our work was supported by the National Natural Science Foundation of China (no. 81201803), the Liaoning Province Science and Technology Plan Project (nos. 2011404013-3 and 2013225079), and the Specialized Research Fund for the Doctoral Program of Higher Education (no. 20122104110028).

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

Variable	*Comparison*	*Patients*	*Univariate*			*Multivariate*		
		(n)	*HR*	*95% CI*	p *Value*	*HR*	*95% CI*	p *Value*
Age	≥60 years vs. <60 years	21/41	1.51	0.67 to 3.40	0.321			
Sex	Men vs. women	44/18	1.64	0.61 to 4.39	0.326			
T Stage	T3 vs. T4	42/20	1.28	0.56 to 2.92	0.560			
N Stage	N0 vs. N1 vs. N2 vs. N3	7/24/21/10	1.63	1.04 to 2.57	0.035			
Histologic grade	G1 vs. G2 vs. G3 vs. G4	12/18/22/10	1.56	1.02 to 2.38	0.042			
Performance status	0 vs. 1 vs. 2	9/45/8	2.14	1.01 to 4.52	0.047			
Chemotherapy regimen	FP vs. CP vs. PD	21/19/17	1.34	0.81 to 2.22	0.250			
Serum C-reactive protein	≤8 mg/L vs. >8 mg/L	44/18	3.55	1.56 to 8.05	0.002	3.04	1.22 to 7.55	0.017

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

8. REFERENCES

1. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet* 2005;365:2041–54.
2. Lu H, Peng L, Yuan X, *et al.* Concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: a treatment paradigm also applicable to patients in Southeast Asia. *Cancer Treat Rev* 2009;35:345–53.
3. Xu T, Zhu G, He X, Ying H, Hu C. A phase III randomized study comparing neoadjuvant chemotherapy with concurrent chemotherapy combined with radiotherapy for locoregionally advanced nasopharyngeal carcinoma: updated long-term survival outcomes. *Oral Oncol* 2014;50:71–6.
4. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. *Br J Surg* 2003;90:215–19.
5. Guillem P, Triboulet JP. Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. *Dis Esophagus* 2005;18:146–50.
6. Zeng YC, Xue M, Chi F, *et al.* C-Reactive protein level predicts prognosis in patients with locoregionally advanced laryngeal carcinoma treated with chemoradiotherapy. *Tumour Biol* 2012;33:891–5.
7. Lin M, Huang J, Zhu J, Shen H. Elevated pre-treatment levels of high sensitivity C-reactive protein as a potential prognosticator in patients with colorectal cancer. *Exp Ther Med* 2013;6:1369–74.
8. Baba H, Kuwabara K, Ishiguro T, *et al.* C-Reactive protein as a significant prognostic factor for stage IV gastric cancer patients. *Anticancer Res* 2013;33:5591–5.
9. Szkandera J, Gerger A, Liegl–Atzwanger B, *et al.* Validation of the prognostic relevance of plasma C-reactive protein levels in soft-tissue sarcoma patients. *Br J Cancer* 2013;109:2316–22.
10. Xia WX, Zhang HB, Shi JL, *et al.* A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment serum C-reactive protein and N-classification. *Eur J Cancer* 2013;49:2152–60.
11. Chen HH, Wang HM, Fan KH, *et al.* Pre-treatment levels of C-reactive protein and squamous cell carcinoma antigen for predicting the aggressiveness of pharyngolaryngeal carcinoma. *PLoS One* 2013;8:e55327.
12. Liao Q, Zeng Z, Guo X, *et al.* LPLUNC1 suppresses IL-6–induced nasopharyngeal carcinoma cell proliferation via inhibiting the Stat3 activation. *Oncogene* 2014;33:2098–109.
13. Yang Y, Zhou H, Li W, *et al.* Lipopolysaccharide (LPS) regulates TLR4 signal transduction in nasopharynx epithelial cell line 5-8F via NFKB and MAPKS signaling pathways. *Mol Immunol* 2007;44:984–92.
14. Ganter U, Arcone R, Toniatti C, Morrone G, Ciliberto G. Dual control of C-reactive protein gene expression by interleukin-1 and interleukin-6. *EMBO J* 1989;8:3773–9.
15. Heikkilä K, Harris R, Lowe G, *et al.* Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. *Cancer Causes Control* 2009;20:15–26.
16. Kinoshita A, Onoda H, Takano K, *et al.* Pretreatment serum C-reactive protein level predicts poor prognosis in patients with hepatocellular carcinoma. *Med Oncol* 2012;29:2800–8.
17. Kasymjanova G, MacDonald N, Agulnik JS, *et al.* The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer. *Curr Oncol* 2010;17:52–8.

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