Original Article

Clinical Implications of C-Reactive Protein as a Prognostic Marker in Advanced Cancer Patients in Palliative Care Settings

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Abstract

Context. Plasma C-reactive protein (CRP) levels are elevated in patients with advanced cancer.

Objectives. To investigate CRP as a prognostic marker in palliative settings.

Methods. This multicenter prospective cohort study comprised 2426 patients. Laboratory data were obtained at baseline, and all patients were followed until death or six months after their enrollment. A total of 1511 patients were eligible for the analyses. They were divided into four groups: low-CRP (CRP $<$ 1 mg/dL), moderate-CRP (1 $\leq$ CRP $<$5 mg/dL), high-CRP (5 $\leq$ CRP $<$10 mg/dL), and very high-CRP (10 mg/dL $\leq$ CRP) groups. Survival was investigated by the Kaplan-Meier method with the log-rank test. The 30-, 60-, and 90-day mortality rates were tested by Chi-squared tests. Univariate- and multivariate-adjusted hazard ratios (HRs) and 95% CIs in each group were calculated using Cox proportional hazard models.

Results. Survival rate decreased and mortality rate increased with increasing CRP level. The differences in survival and 30-, 60-, and 90-day mortality rates among the groups were statistically significant ($P < 0.001$). Baseline CRP level was significantly associated with a higher risk of mortality after adjustment for age, gender, primary tumor site, metastasis, chemotherapy, Eastern Cooperative Oncology Group Performance Status, and setting of care (moderate-CRP: HR 1.47 [95% CI 1.24−1.73], high-CRP: HR 2.09 [95% CI 1.74−2.50], and very high-CRP: HR 2.55 [95% CI 2.13−3.05] vs. low-CRP).

Conclusion. Clear dose-effect relationships between elevated CRP levels and prognoses indicate that CRP could be useful in predicting prognoses in patients with advanced cancer. J Pain Symptom Manage 2016;■:■−■.

Key Words

C-reactive protein, prognostic marker, advanced cancer patients, palliative setting

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Accepted for publication: December 1, 2015.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2015.11.025

Introduction

C-reactive protein (CRP) is a classical acute-phase protein displaying a rapid and pronounced rise of its plasma concentration in response to acute inflammation, for example, infection and tissue damage.[1–3] Plasma CRP levels are also moderately elevated in response to chronic inflammatory diseases and cancer.[1–3] Recent epidemiologic studies suggest that elevated CRP levels not only mark the presence of prevalent cancer but also are associated with an increased risk of future cancer in apparently healthy individuals.[1–3]

Several studies reported an association between elevated CRP levels and poor prognoses in patients with several types of solid cancer receiving surgery, chemotherapy, or radiotherapy, with a broad variance of malignancies.[2–18] Additionally, some tumors that synthesize CRP are known to be associated with poor outcomes.[19,20] Thus, not only plasma CRP levels but also intratumoral CRP expression may be a useful tool for predicting prognosis. However, it remains unknown if circulating CRP is produced by the tumor, liver, or both.[21]

The combined evidence suggests that elevated CRP levels are associated with poor prognoses independent of tumor stage, and thus elevated CRP levels seem to be associated with poor prognoses in advanced cancer patients.[2–4,22–24] In addition, the combined use of interleukin-6 (IL-6) and CRP as a marker of inflammation associated with cancer cachexia might provide better prediction in patients with advanced cancer. However, measurement of plasma IL-6 and other cytokines, that is, IL-1 and tumor necrosis factor alpha (TNF-α), is difficult because of their short plasma half-lives and the high cost of such an approach. This makes CRP the preferred marker in those with advanced cancer.[25]

Nonetheless, to the best of our knowledge, there have been no large prospective studies investigating the clinical implications of CRP as a prognostic marker in advanced cancer patients in a variety of palliative settings, including palliative care units, hospital palliative care teams, and home palliative care services, as well as in patients receiving chemotherapy. This study was, therefore, designed to investigate the clinical implications of CRP as a prognostic marker in advanced cancer patients in palliative settings.

Methods

This study involves a subanalysis of a multicenter prospective cohort study conducted in 58 palliative care services in Japan from September 2012 through April 2014.[26,27] The participating units included 16 palliative care units, 19 hospital palliative care teams, and 23 home palliative care services. Patient demographics, clinical characteristics, including gender, site of primary cancer, metastatic disease, and chemotherapy in past 30 days, and laboratory data were obtained on the first day of admission. Plasma CRP levels were determined with examination of fresh plasma samples using latex-enhanced immunoturbidimetric assay (i.e., IATRO CRP-EX [LSI Medience Corporation, Tokyo, Japan]). All samples were analyzed with an automatic serum analyzer (e.g., LABOSPECT 008 [Hitachi, Tokyo, Japan]) at a central laboratory of each institution. The coefficient of variation was <10%.

Consecutive eligible patients were enrolled in this study if they had been newly referred to the participating institutions during the study period. All institutions were asked to take a sample of data consecutively, up to the designated number of patients of 20, 40, 60, 80, or 100 according to the size of the institution. Inclusion criteria for this study included adult patients, patients diagnosed with locally extensive or metastatic cancer (including hematologic neoplasm), and patients admitted to palliative care units, receiving help from hospital palliative care teams or receiving home palliative care services. Patients who died of unexpected complications, such as infection, bleeding, unexplained cardiac arrest, and cardiovascular complications, were excluded.

All interventions and observations were conducted within routine clinical practice (i.e., no extra blood tests were allowed). This study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for epidemiologic research of the Ministry of Health, Labor and Welfare in Japan. Written consent was unnecessary. The local institutional review boards of all participating institutions approved this study.

Statistical Analyses

Patients were divided into four groups according to baseline CRP values. Comparisons among the groups were made by using analysis of variance, the Kruskal-Wallis test, or the Chi-squared test as appropriate.

Survival after enrollment was investigated by the Kaplan-Meier method using the log-rank test. The *P*-value for the log-rank test was used to examine whether survival time differed between the groups. The 30-, 60-, and 90-day mortality rates in each group were visualized by using bar plots. The differences in the 30-, 60-, and 90-day mortality rates between the groups were tested by Chi-squared test. Univariate- and multivariate-adjusted hazard ratios (HRs) and 95% CIs in each CRP group were calculated by using Cox proportional hazard models.

In the multivariate model, we included the following variables as covariates: age, gender,