The Role of C-Reactive Protein as a Prognostic Indicator in Advanced Cancer

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C-reactive protein (CRP) is a nonspecific but sensitive marker of inflammation. Interleukin-6 (IL-6), IL-1, and tumor necrosis factor α induce the synthesis of CRP in hepatocytes. Increased CRP level is considered to be an important risk factor for atherosclerosis, myocardial infarction, peripheral vascular disease, and ischemic stroke. It is positively correlated with weight loss, anorexia–cachexia syndrome, extent of disease, and recurrence in advanced cancer. Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors. Measurement of CRP is simple, cheap, and routine and provides valuable information in palliative care.

Introduction

Researchers in palliative medicine have always shown an interest in determining chances for survival because this is an important consideration in selection between active intervention and palliation in patients with advanced cancer [1••]. To determine the chance of survival, physicians now use several prognostic factors including the Karnofsky and Eastern Cooperative Oncology Group (ECOG) functional scales, tumor stage, and a combination of biologic and nutritional factors. Recently, C-reactive protein (CRP), a member of a group of biologic substances called the acute-phase protein response, has been found to be a prognostic indicator of inflammation in various pathologies. Clinical studies are now trying to clarify its role in advanced cancer [2].

C-Reactive Protein

CRP was first discovered in 1930 by Tillett and Francis, who noticed its ability to bind to the C-polysaccharide component of the pneumococcal cell wall. Since its discovery, CRP has become a nonspecific, but sensitive marker of inflammation. Its synthesis in hepatocytes is induced by pro-inflammatory cytokines, mainly interleukin-6 (IL-6) and, to a lesser extent, IL-1 and tumor necrosis factor alpha (TNF-α) [2,3]. The production of CRP increases within 4 to 6 hours after the onset of inflammation, doubles every 8 hours thereafter, and peaks at approximately 36 to 50 hours. Levels remain elevated with ongoing inflammation and quickly return to normal once inflammation is resolved. The rapid kinetics of CRP metabolism, which closely parallel the inflammatory course, supports its value as an acute measure of disease activity. CRP is superior to other acute-phase protein reactants (APPR), for which the phase of rise is much slower [3,4•,5]. Although CRP has both proinflammatory and anti-inflammatory functions, its net effect is anti-inflammatory because it prevents the adhesion of neutrophils to endothelial cells, inhibits the generation of superoxide by neutrophils, and stimulates the synthesis of IL-1–receptor antagonists by mononuclear cells.

A number of epidemiologic studies have shown elevated CRP levels to be an important risk factor for atherosclerosis, myocardial infarction, peripheral vascular disease, and ischemic stroke [5–7]. Kushner [8••], discussed the modest elevations of CRP in non-inflammatory conditions, including obesity, depression, chronic fatigue syndrome, and sleep disturbance. Furthermore, Kushner suggested its possible role as a marker of biologic aging, a condition associated with poor prognosis and death.

Recent research has focused on therapeutic modification of elevated CRP levels. Short-term administration of ibuprofen in cancer patients significantly reduces plasma levels of CRP [9,10••]. Previous studies suggested that histamine enhances murine IL-6–induced CRP synthesis by hepatocytes [11]. Ramussen *et al.* [12] studied the effect of preoperative ranitidine, a histamine-2 receptor antagonist, on postoperative plasma levels of IL-6 and serum CRP in women (n=32) undergoing elective abdominal hysterectomy. IL-6 levels significantly increased in all patients, without any difference between ranitidine-treated and untreated patients. 48 hours after surgery, CRP was significantly reduced in ranitidine-treated patients, suggesting that ranitidine modulates IL-6 effect on hepatic cells.

CRP and survival

The significance of CRP as a predictor of survival has been shown in multiple myeloma [13], melanoma [14],

lymphoma [15], ovarian [16••,17], renal [18], gastrointestinal [19,20], and pancreatic cancer [21,22] (Table I). Between the time of diagnosis and the time of death in patients with advanced pancreatic cancer, there is a significant rise in the number of patients exhibiting an APPR, as defined by increased CRP and decreased serum albumin [21,22]. This APPR is associated with poor prognosis and appears to be independent of other conventional prognostic factors, such as age, sex, and stage of disease [22].

The pattern of weight loss in patients with advanced pancreatic, esophageal, and lung cancer is relatively linear and parallels the pattern of elevation of CRP levels [21,22]. O'Gorman *et al.* [20] assessed several prognostic factors in patients with advanced gastrointestinal cancer (n=91) and found that CRP, metastases, and Karnofsky performance status had independent prognostic value.

Geissbuhler *et al.* [1••] reported a positive correlation between CRP, vitamin B_{12}, and survival in consecutive, terminally ill cancer patients (n=161), with a median age of 74.7 years. Multivariate analysis revealed CRP to be the most important prognostic factor. This study indicates that vitamin B_{12} is an independent predictive factor for mortality in patients with advanced cancer.

IL-6 promotes coagulation in experimental animals [27]. CRP stimulates tissue factor production and neutrophil aggregation [28]. This could indicate a direct contribution of IL-6 and CRP to mortality [29]. High IL-6 levels may also reflect cellular damage, such as oxidative stress [30].

CRP and the anorexia–cachexia syndrome

Cachexia, the most common cause of death in advanced cancer [31], is not only weight loss but also involves a cluster of both symptomatic and biochemic abnormalities. The symptom cluster includes anorexia, early satiety, muscle wasting, asthenia, fatigue, anemia, edema, and taste changes [31,32••]. The biochemical cluster involves decreased lipoprotein lipase activity and increased plasma leptin, IL-1, IL-6, TNF-α, and CRP [31, 32••, 33, 34].

The significant correlation between serum IL-6 and CRP has been demonstrated in malignancy [14,22, 29,35]. Barber *et al.* [22] compared both levels among patients with advanced pancreatic cancer (n=13) and healthy control patients (n=6). In the cancer group, median CRP and IL-6 levels were 5.4 mg/L and 5.2 pg/mL respectively, compared with levels of less than 1 mg/L and less than 0.5 pg/mL in the control group. Oka *et al.* [36] reported in 1996 that CRP levels were significantly higher in esophageal squamous cell carcinoma patients who had serum IL-6 levels of 7 pg/mL, compared with patients who had serum levels less than 3 pg/mL. Four mechanisms that may explain the role of CRP and cytokines in the anorexia–cachexia syndrome are described in the following sections.

Cytokine-induced muscle wasting

Proinflammatory cytokines directly affect muscle breakdown by increasing the loss of body cell mass. TNF-α produces most of the features of cachexia when administered to humans [37]; however, significant serum levels are rarely detected in patients with cancer, suggesting that local production might be more important to the regulation of the acute APPR than are serum levels [18,20–22,34,35,38].

CRP-induced metabolic changes

The persistence of the APPR, seen in patients with cancer and AIDS, can lead to a metabolic disturbance that eventually results in cachexia. Decreased food intake, common in patients with advanced cancer [32], reduces amino acid supply. The increased demand, an ongoing inflammation with persistent production of the APPR, will result in reprioritization of amino acid metabolism away from peripheral tissues, especially muscles, towards the liver. The result is persistent skeletal muscle catabolism and wasting [2,21,39,40].

Decreased lipoprotein lipase activity

The activity of lipoprotein lipase (LPL), a key regulatory enzyme for triglyceride clearance from plasma, is reported to decrease as tumor burden increases in tumor-bearing animals and in patients with lung, gastrointestinal, and breast cancer. Therefore, it is believed to play a key role in inducing cancer cachexia [41,42].

Induction of lipolysis by cytokines is thought to result from inhibition of LPL. IL-6 has been documented to reduce LPL activity in tissue, whereas TNF-α has been shown to reduce LPL activity, decrease fat deposits, induce emaciation, and worsen cachexia [43].

Metal-binding protein

IL-6 increases the production of metallothionein, a metal-binding protein, resulting in enhanced zinc binding and, consequently, hypozincemia. The latter has been reported to be a possible cause of taste changes in patients with advanced cancer [44,45].

The combined use of IL-6 and CRP as indicators of inflammation associated with the anorexia–cachexia syndrome may provide a better prediction of outcome in patients with advanced cancer. However, measurement of plasma IL-6 and other cytokines is difficult because of short plasma half-life, presence of blocking factors, high cost, and limited availability. This makes CRP the preferred marker of the inflammatory process in patients with advanced cancer [6,21,22,46].

CRP and tumor recurrence

Wigmore *et al.* [47••], followed CRP levels in patients with colorectal cancer (n=202) prior to and after surgery. Thirty-six percent of the patients had levels greater than 10 mg/L before surgery. Following tumor resection, the proportion of patients with levels of 10 mg/L or more decreased to 5%.

Table 1. The correlation between C-reactive protein and survival

Study	Diagnosis	Patients, *n*	CRP, *mg/L*	Survival, *y*	Survival rate, %	Conclusion
Falconer *et al.* [21]	Pancreatic cancer*	57	<10	0.6	56	CRP is a useful prognostic indicator in pancreatic cancer
		45	>10	0.1	44	
Nozoe *et al.* [23]	Colorectal cancer	50	>8	1	68.7	Preoperative serum elevation of CRP is an indicator of the malignant potential of a tumor
				2	47.3	
				3	47.3	
	Colorectal cancer	70	<8	1	94.8	In addition to serving as an indicator of malignant potential, CRP is a predictor of the prognosis in colorectal cancer
				2	89.8	
				3	83.5	
Kodama *et al.* [16••]	Ovarian cancer	89	<50	5	56.7	CRP is an adverse prognostic factor in univariate but not mulitvariate analysis
		31	>50		11.1	
Fujikawa *et al.* [50]	RCC, surgery	13	>1	1.9	—	Cytoreductive surgery is beneficial in those patients with elevated preoperative serum CRP levels; those patients in whom CRP levels decrease to normal may expect to live longer
	RCC, no surgery	21	>1	0.6	—	
	RCC, surgery	13	<1	3.7	—	
	RCC, no surgery	8	<1	2.5	—	
Miyata *et al.* [24]	RCC	52	Normal	5	82.7	The log-rank test revealed that levels of CRP and ferritin significantly influenced survival
		40	Elevated		62.5	
Vesole *et al.* [25]	MM, underwent autotransplant	242	<4	5.5	—	Low B_2-microglobulin and CRP levels <0.4 mg/dL were the most significant standard parameters associated with prolonged survival
		228	>4	3	—	
Kato *et al.* [39]	NSCC	127	<2	2	—	Serum CRP is an independent survival determinant in advanced NSCC of the lung
			>3	0.3	—	
Ueno *et al.* [57]	Pancreatic cancer	103	<50	0.3	—	CRP, performance status, and CA19-9 level were identified as significant prognostic factors in metastatic pancreatic carcinoma
			>50	0.14	—	
Legouffe *et al.* [15]	NHL	23	<10	>2.6	75	CRP may be considered as a valuable and easy prognostic biomarker of NHL.
		16	>10	0.7	—	
Bataille *et al.* [26]	MM	162	<6	4.5	50	CRP level is a highly significant prognostic factor
			≥6	2.25	35	
				0.5	15	

*All are advanced cancer.
CA 19-9—tumor marker for pancreatic carcinoma; CRP—C-reactive protein; MM—multiple myeloma; NHL— non-Hodgkin's lymphoma; NSCC—non–small-cell carcinoma; RCC—renal cell carcinoma; y—years.

This suggests that the presence of the primary tumor is associated, directly or indirectly, with CRP production. Either the primary tumor itself or the inflammatory response associated with it is responsible for cytokine production with enhanced CRP production. This implies possible utility of CRP as an index of tumor recurrence [21,48••,49].

Preoperative elevation of CRP level is associated with increased recurrence after curative colorectal cancer resection surgery, compared with normal preoperative levels [47–49]. Postoperative increase in CRP level is due to persistent production of IL-6 by metastases and is a marker of recurrence. For these reasons, measurement of CRP may have clinical potential as a predictor of cancer recurrence and survival [50]. McMillan *et al.* [49] reported tumor recurrence in 73% of patients with CRP levels that were greater than 5 mg/L prior to surgery and recurrence in 10% of those with CRP levels that were less than 5 mg/L. However, the results of Wigmore *et al.* [47••] are contradictory. They found that there was no difference in recurrence rates after surgery between those patients with increased (40%) and those patients with decreased (36%) preoperative levels of CRP.

CRP and extent of disease

The hypothesis that serum CRP level might be an indicator of the extent of and of the malignant potential of cancer appears to be valid. This has been widely reported in gastrointestinal neoplasms [40,47••,51]. Nozoe *et al.* [23] studied consecutive patients with colorectal cancer (n=127) and found that the incidence of liver metastases, peritonitis carcinomatosa, enlarged lymph nodes, and intravascular invasion in those patients with preoperatively elevated serum CRP levels were significantly more frequent, compared with those with lower levels.

According to earlier studies, the serum CRP level in patients with cancer is dependent on the tumor load, being higher in patients with metastases than in those patients with local disease [19,20,22]. There is a positive correlation between the volume of liver metastases in colorectal cancer and the serum level of IL-6 that stimulates hepatic CRP production. It can be argued that increased tumor bulk provides a greater potential for tumor necrosis and inflammation; thus serum CRP may simply reflect tumor burden [20,40,47••,49].

CRP and infection

Patients with advanced cancer are vulnerable to various infections that negatively affect outcome and increase mortality. Recently, IL-6, TNF-α, and soluble TNF receptors were identified as early and sensitive markers of severe infections in both non-neutropenic patients and immunosuppressed cancer patients [53]. Several studies showed that follow-up levels of CRP typically decrease in cancer patients with solid tumors and treated infections [54]. Similar results have been obtained in patients with neutropenic fever [55]. On the other hand, follow-up levels in neoplastic fever remain unchanged. This can be used as a supplementary method to naproxen test in the differential diagnosis of neoplastic fever [56].

Conclusions

Predicting survival is very important in palliative care, as it assists physicians in making appropriate clinical decisions and choosing treatment strategies. If physicians accept death as part of the natural progression of terminal disease, overtreatment and overdiagnosis can be avoided. CRP has been used as an independent prognostic indicator in studies of several diseases, including multiple myeloma, lymphoma, melanoma, and ovarian, renal, pancreatic, and gastrointestinal tumors. Increased CRP levels detected in patients with advanced cancer may predict several serious conditions including the anorexia–cachexia syndrome, tumor recurrence, extent of disease, and infections, which decrease chances of survival. Further research is mandatory because therapeutic modifications of inflammation or CRP might promote weight gain and improve quality of life in patients with advanced cancer.

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