Value of CRP as a Marker of Infection in Cancer Patients with Febrile Neutropenia: Review

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Abstract: Cancer patients often suffer from deficiency of immunity and increased susceptibility to infection. Neutropenia is the most serious hematologic toxicity of cancer chemotherapy, often limiting the doses of chemotherapy that can be tolerated and puts patients at risk of severe infection. Infections are among the most common cause of death and potentially serious complications of cancer and its treatment. Neutropenia with fever (Febrile neutropenia) is a well-recognized and potentially life-threatening complication of cancer chemotherapy that is considered as medical emergency requiring prompt in-hospital evaluation and administration of adequate treatments. Tumor associated fever can arise from either infection or its underlying treatment such as radiotherapy and chemotherapy as wells by production of pyrogenic cytokines in cancerous cells. Distinguishing between infectious fever and non-infectious fever is of paramount importance in cancer patients because of the urgency and necessity for appropriate treatment in these high risk and immunocompromised individuals. The relatively robust and reliable response to inflammation makes C-reactive protein (CRP) an ideal marker for inflammation and infection in febrile neutropenic cancer patients. Determination of serum CRP levels in febrile neutropenic patients is also helpful in the differential diagnosis of bacterial and viral infections as well as its serial measurements are used to monitor treatment effectiveness.

Key words: cancer; chemotherapy; immunity; neutropenia; infection; fever; C - reactive protein

Introduction

Cancer is now the world's leading cause of death, accounting one in eight deaths overall-more than AIDS, tuberculosis, and malaria combined. In 2004 there were 7.4 million deaths globally, in 2007 it was 7.9 million deaths and in 2010 it took the first place in the causes of death with over 8 million deaths worldwide [1]. The frequency of cancer patients requiring intensive care has increased dramatically over the last decades. Frequently, in these patients, combined mechanisms of immune-suppression coexist resulting in an increased risk for sepsis. Infection is a feared and life-threatening complication in cancer patients, in particular if neutropenia is present, that is frequently related to cancer treatments, either radiation or chemotherapy [2]. The purpose of this review was to analyze the association between cancer and infection susceptibility and to evaluate the effectiveness of CRP in predicting the presence and severity of infection as well as its ability to monitor responses to antimicrobials.

Cancer and immunomodulation

The interaction of the immune system with the malignancy is an ongoing dynamic process where immunity is modified by the tumor and the tumor in turn is modified by the immune system. The immune system is fully capable of killing tumor cells, but it has difficulty in recognizing them due to tumor-induced immune suppression [3]. Generally cancer patients face immune system challenges in fighting malignancies through immune mechanisms and confronting the immune-suppressive effects of the disease and its treatments [4]. Tumors have developed strategies to successfully evade and escape the host immune system, and various molecular and cellular mechanisms responsible for tumor evasion and escape have been identified [3,5].Cancer induces deleterious effects on the host immune system starting from alterations in lymphocyte homeostasis to functional disability or even elimination of effector cell subsets. These tumor-induced effects are variable, persistent and long-lasting [5].

Anticancer drugs that destroy cancer cells by stopping them from growing or dividing at one or more points in their growth cycle also kills rapidly dividing healthy normal cells. Among these rapidly dividing healthy cells are leukocytes and bone marrow precursors, and therefore chemotherapies are generally considered to be immunosuppressive [5, 5, 6].Because many anticancer chemotherapy agents also cause DNA damage they can have a profound effect on proliferating lymphocytes as well as affecting generation and function of antigen-presenting cells (monocytes, macrophages, dendritic cells and B cells) derived from hematopoietic stem cells [6]. Finally Cancer cells can also release chemicals that change normal immune cells [7].

Infection susceptibility and complication in cancer patients

It has been estimated that 75% of all deaths in acute leukemia are attributable to infection, while the corresponding figure in patients with solid tumors is 50 % [8]. Infections are among the most common, potentially serious complications of cancer and its treatment. Infections that develop in people with cancer or are getting cancer treatment can be more serious than those developing in healthy people [9]. Defects of the immune response against infection arise from several factors acting either concomitantly or sequentially; certainly, major roles are played by the underlying cancer disease its treatment. Disruptions of physical defense barriers like skin or mucosae by chemotherapy, tumor growth, and/or the frequent use of venous access catheters lead to a disturbed balance between host defense and exposure to potentially pathogenic microorganisms [9]. Cytotoxic chemotherapy predictably suppresses the hematopoietic system and impairing host protective mechanisms [10]. The majority of infections in cancer patients results from invasiveness of microorganisms that are part of the normal host flora colonizing skin and gastro-intestinal mucosae. Damage to the gastro-intestinal mucosa cells, for example, predispose to the process of bacterial translocation, in which bacteria from the lumen of the intestine invade the blood and regional lymph nodes [11,12] While individual agents clearly have immediate effects on immune function, the widespread approach of treating both hematological and non-hematological malignancies with repeated cycles of chemotherapy given over many months has a prolonged and profound suppression of cell mediated immunity [6,13].

Development of immunity and defense against infection is initiated by macrophage activation that is induced by inflammation resulting from the infection. Membranous lipid metabolites of inflamed normal and cancerous tissues, lysophospholipids and alkylglycerols, are potent macrophage-stimulating agents. Studies showed that cancer patients, but not the healthy humans, carried plasma α-N'-acetyl galactosaminidase which inactivates these macrophage activation factor (MAF) synthesis in B and T cells. Because macrophage activation is the first step in the inflammation primed immune development cascade, such cancer patients become immunosuppressed and therefore explains partly why cancer patients die from overwhelming infection [7,14].Another in *vitro* experiment using whole blood cultures from cancer patient showed that diminished production of early pro inflammatory cytokines(IL-6, IL-8 IL-1 and TNF) due to a decreased number of circulating white blood cells as result of hematopoietic and immune suppression by chemotherapy used or the underline disease [11].

Infection susceptibility in neutropenic cancer patients

Neutropenia, defined as neutrophils count less than 500 cells/mm3, reflects a profound state of immune-suppression and signifies a markedly increased susceptibility to infections [9]. It is the single most important predisposing factor to infection in the person with cancer and infection is the most common cause of death in the cancer patients [10].

Patients have an increased risk of bacterial infection not only by common bacteria, but also by opportunistic agents, like virus and fungi, secondary to a decrease cellular and humoral immunity. In addition, the size of the inoculum necessary to produce an infection is reduced in neutropenic patients [15,16]. Cyclic chemotherapy and radiotherapy suppresses the normal production and subsequent availability of neutrophils to fight infection. Consequently chemotherapy-induced neutropenia (CIN) is most serious hematologic toxicity of cancer chemotherapy, the major dose-limiting toxicity of systemic cancer chemotherapy, and it is associated with substantial morbidity, mortality, and costs[9,10,17]. The effects of chemotherapy on bone marrow's ability to maintain production of an adequate amount of neutrophils may result in severe neutropenia with or without fever [18,19].

Febrile neutropenia

The relationship between fever, neutropenia, bacteremia, and sepsis has been widely known for more than 40 years [20]. Febrile neutropenia is a well-recognized and potentially life-threatening complication of cancer chemotherapy that is considered as medical emergency requiring prompt in-hospital evaluation and management [21,22]. Neutropenia blunts the inflammatory response to nascent infections, allowing bacterial multiplication and invasion. It is associated with a profound impairment in the inflammatory response leading to a reduction of the usual signs and symptoms of infection such as erythema, swelling, heat, pain and pus formation. Because neutropenia reduces the signs and symptoms of infection, patients with neutropenia often may present with fever as the only sign of infections [18,23,24]. However, a wide range of biologic processes, infectious (such as viruses, bacteria, fungi) and many noninfectious (such as drugs, toxins, tumors, cytokines etc.) can cause temperature elevation [18, 23]. Recently it has been shown that the cause of fever in febrile neutropenic cancer patients is microbiologically defined infection in 44% (of which cases 80% are bacteremia), clinically defined infection in 17% and unknown in 39% [8].

Tumor associated fever can arise from either infection or its underlying treatment such as radiotherapy and chemotherapy. Even more fever can be follow diagnostic or therapeutic procedures, medication, transfusion, surgery act and other technical procedures. On the other hand, some tumor causes fever through necrosis such as large tumor or metastasis or production of pyrogenic cytokines (IL-1,IL-6, TNF, and INFs) [25,26,27].

Distinguishing between infectious fever and neoplastic fever is of paramount importance in cancer patients because of the urgency and necessity for appropriate treatment in these high risk individuals. Management of patients will be also different based on the origin of fever.

Diagnosis challenges in febrile neutropenia cancer patients

The search for a suitable biomarker which indicates immune system responses in cancer patients has been long and arduous. Because infection has been the most common cause of death in neutropenic cancer patients, a large number of studies have focused on the diagnosis and management of neutropenic infections in pediatric and adult cancer patients [8]. The differential diagnosis of infections in febrile neutropenic cancer patient is a daily problem in oncologic clinical work. Symptoms typical of infection, such as fever and changes in the laboratory parameters, can be caused equally well by the underlying malignancy or its treatment [8, 28] or these signs may be minimal to totally absents and fever could be the only clinical sign, but it can be caused by non-infectious causes as well [28].The white blood cell count (WBC) is also not useful since it can also be markedly influenced by the cancer itself as well as by the exposure to corticosteroids and chemotherapy. A positive blood culture usually requires 24 hours or longer before results can be obtained [28, 2]. As a result early identification and manifestations of infection are often challenging and misleading, in particular in the presence of neutropenia. Moreover, untreated infections in cancer patients can rapidly lead to a fatal outcome but, treating non-infectious causes with antimicrobials is ineffective, delays the correct treatment of the underlying disease and also increases costs, toxicity and the risk for the development of bacterial resistance to antibiotics [29,30].

Physicians are therefore always on the alert for a method that promises to be either sensitive or specific for the detection of infection: one that would be helpful in the difficult decision whether to institute antibacterial therapy or not.

C - reactive protein

C Reactive Protein (CRP) is one of the earliest known and mostly used acute-phase plasma proteins that can be used as a marker for activation of the immune system since 1930[31]. When the body encounters stress such as disease, infection, inflammation, chemical or physical trauma, the body's natural defense system is triggered by these stress factors which in turn induced the secretion of cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor (TNF) to increase the production of CRP in the liver [31, 32].CRP was discovered by Tilled and Francis in 1930 in the blood of patients with *Streptococcus pneumonia* infection. Named for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumonia*, CRP was the first acute-phase protein to be described and is an exquisitely sensitive systemic marker of inflammation and tissue damage [15,31,33]. C-reactive protein has long been recognized as an innate opsonin, that is, a protein that recognizes microbes and promotes their uptake by phagocytic cells. The prototypic ligand of CRP is phosphocholine (PC), to which CRP binds in a calcium-dependent manner. Phosphocholine (PC) is a component of most biological cell membranes and many bacterial and fungal polysaccharides [34]. Recognition of ligands by CRP promotes phagocytosis in two ways. First, ligand-complexed CRP binds C1q and activates the classical human complement pathway, leading to the deposition of opsonic complement fragments. Second, CRP interacts directly with phagocytic cells through Fcγ receptors (FcγRs). Thus, CRP functions as a first line of innate host defense by binding to a number of pathogens and promoting their elimination by phagocytic cells [35, 36]. CRP has also key role in facilitating the removal of damaged cells. It is found that in addition to binding to lysed or permeabilised cells, CRP binds to the membranes of intact apoptotic cells. The increased CRP was associated with enhanced phagocytosis of the apoptotic cells and would thus contribute towards their clearance [34].The ability of CRP to recognize disease-causing agents and damaged cells and to mediate their removal highlights its crucial role in innate immunity.

CRP as a marker of inflammation and infection

CRP determination has been used in the diagnosis of infection as well as to monitor the outcome of infection treatment in patients with hematological and pediatric malignancies with profound neutropenia [8].The relatively robust and reliable response to inflammation makes CRP an ideal candidate marker for inflammation and infection in febrile neutropenic cancer patients [31, 37].CRP rises above normal levels rapidly within 6 hours, peaking at about 48 hours. The half-life of CRP is about 19 hours and relatively constant, so that levels fall sharply after initiation unless the plasma level is maintained high by continued CRP production in response to continued antigen exposure and inflammation.

Recent observations have shown that CRP, when compared with ESR and WBC count, may be the most useful and versatile marker of inflammation and its serum concentration and secretory levels remain unaltered by eating and display little or no interference by most drug administration unless, of course, they alter the inflammatory stimulus. It has been shown that among septic critically ill cancer patients a marked increase in CRP concentrations irrespective of the white blood cell count and immunosuppression, indicating that the acute phase reaction seems to remain unaffected by either chemotherapy or radiotherapy. Moreover, it was found that septic neutropenic cancer patients had significantly higher CRP concentrations in comparison with non-

neutropenic patients. In this context, it is hypothesized that microbiological agents would invade and proliferate easily in neutropenic patients, reaching a higher microbiological burden and also leading to a larger inflammatory response, reflected by a higher CRP concentration[16,38]. Conversely, ESR can be influenced by sex, inflammation, estrogen status, immunoglobulin levels, hyperlipidemia, hypoalbuminemia, severe anemia and the number and morphology of red blood cells present [38].

CRP rises up to 5000 fold in acute inflammation, such as severe acute infection or trauma. In most situations, the factors controlling CRP release and regulation are essentially those controlling inflammation or tissue injury. It is therefore relatively tightly regulated depending on the presence and degree of inflammation, with typical rises and falls in plasma CRP levels, forming a characteristic homeostatic, oscillatory cycle when inflammation occurs [31].Serum levels of CRP have been determined in healthy individuals, and these values have proven to be uniformly low (10 mg/L) in the absence of infection. Serum CRP levels of >40 mg/L have been shown to be sensitive markers for systemic bacterial infections in both adult and pediatric immune-competent individuals with fever [29]. Generally, CRP is highly elevated by serious bacterial infections (any potentially life-threatening bacterial infection, such as meningitis or pneumonia), up to 150–350 mg/L making it an attractive diagnostic test for sepsis [39]. But it is less elevated by acute viral infection, to 20–40 mg/L. This is very crucial in differential diagnosis of bacterial and viral infections. However, this is not absolute: some viral infections can cause elevations >100 mg/l (e.g., adenovirus, mumps and measles) and intermediate CRP concentrations (10–50 mg/L) may be seen in both bacterial and viral conditions [29]. But a normal CRP is unlikely in the presence of significant bacterial infection [24, 40]. However, its concentration does not significantly increase until 24 to 48 hours after the onset of inflammation and serum concentrations of CRP are proportional to the degree of tissue damage and the activity of the basal malignant disease [28].

The serial study of CRP value is of considerably greater value in diagnosis, and as a guide to therapy, than single estimations [41]. As elevation of CRP did not always occur in parallel with a rise in temperature during episodes of infection, serial CRP measurement justifies presence or absence of infection. A further rise in CRP level, when already greater than 100 mg/l, may reflect the development of new infection. Increasing CRP values were also directly associated with the number of days with fever during hospitalization and with mortality from infection. The CRP level should, therefore, continue to be studied serially even when greater than 100 mg/l since a failure to fall, or further elevation, can indicate a need for the antibiotics to be changed or for a granulocyte transfusion to be added. On the other hand serial measurements of C-reactive protein with two consecutively low measurements uses as good negative predictive value for the presence of bacterial infection and stable [8,28,42].

Even though CRP measurement has been used in diagnosis, severity evaluation, outcome prediction, and assessment of therapeutic responses of infectious disease, there are some inconsistencies and limitation. Few recent studies suggested that utilization of other infection markers such as pro calcitonin (PCT) and IL-8 might be more reliable than CRP in early evaluation of infections in febrile neutropenic cancer patients [8,43]. CRP levels are also probably raised in any inflammatory process, whether infective or not [44, 45]. In other word it has been postulated that serum CRP levels can be elevated as a consequence of the malignant process itself, irrespective of the presence of a systemic bacterial infection [29]. Even though the role of CRP determination in early prediction of bacteremia still remains controversial, there are only a few studies concerning CRP as a marker of infection in patients with solid tumors and non-neutropenic infections [8])**.** Also evaluation of CRP in different clinical setting is a recent issue attracting several researchers.

Conclusions and Recommendations

In neutropenic cancer patients with fever identification and treatment of infection is always challenging and confusing due to the absence of underline sign and symptom of infection. Untreated infections can rapidly lead to a fatal outcome but, treating non-infectious causes with antimicrobials is ineffective, delays the correct treatment of the underlying disease and also increases costs, toxicity and the risk for the development of bacterial resistance. Recent data showed that in a substantial amount of patients the fever episode was not accompanied by clinical manifestations of infection suggesting that this group of patients may be over treated.

As a result use of infection biomarkers that can resolve the origin of fever and predict infection at early stage in these patients is urgently needed and should be incorporated in clinical assessments. In this regard the use of CRP as an infection biomarker in neutropenic cancer patients with fever is incredible and evidences supported to practice it in early evaluation and management of infections. When used in conjugation with clinical assessments, CRP measurement is a useful tool for evaluating and resolving possible infective and inflammatory diseases. However as any diagnostic test, false positive and false negative can occur and no test represents a replacement a through clinical review.

Acronyms:

APPs: acute phase proteins, CIN: chemotherapy induced neutropenia, CRP: C-reactive protein , DNA: deoxy ribonucleic acid, ESR: erythrocyte sedimentation rate ,FUO : fever of unknown origin, IL -6: interleukin-6, IL-1: interleukin-1, IL-8:interleukin-8,:INF: interferons, LPS : lipopolysaccharides, MAF, macrophage activation factor, PCT: procalcitonin, STREM-1: soluble triggering receptor expressed on myeloid cells-1, TNF: tumor necrosis factor, WBC: white cell count.

Acknowledgements

The author is grateful to Mr. Balew Arega and Dr. Daniel Seifu for their valuable comments and unreserved supports throughout the manuscript preparation.

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