TRADITIONAL AND NEW MARKERS OF INFECTION IN ADULT CANCER PATIENTS AND THE POSSIBLE INTERFERING EFFECT OF UNDERLYING MALIGNANCY ON THESE MARKERS

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Abstract

The purpose of the present study was to compare the procalcitonin (PCT), neopterin, interleukin-8 (IL-8), interleukin-10 (IL-10) and interleukin-12 (IL-12) levels with those of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in cancer patients with (56) and without infection (36) and to evaluate their ability to differentiate infections from neoplastic fever (n=10).

The infection group had statistically higher levels of CRP (91 vs. 19 mg/l, $p < 0.001$), PCT (0.28 vs. 0.12 ng/ml, $p < 0.001$), neopterin (12.8 pg/mL vs. 4.0 pg/mL, $p < 0.001$), IL-8 (27.7 vs. 16.9 pg/ml, $p = 0.032$), IL-10 (3.8 pg/mL vs. 1.8 pg/mL, $p = 0.005$) and ratios of neopterin to IL-12 (1.74 vs. 0.11, $p < 0.001$), and IL-10 to IL-12 (0.4 vs. 0.05, $p < 0.001$) than the non-infection group. After a subdivision of the study population into patients with local or advanced disease, the differences between the study groups remained statistically significant for CRP and neopterin both in local ($p < 0.05$ and $p < 0.001$) and advanced diasease ($p < 0.01$ and $p < 0.001$) and in advanced disease for PCT ($p < 0.001$), IL-10 ($p < 0.05$), IL-12 ($p < 0.05$), neopterin to IL-12 ratio ($p < 0.01$) and IL-10 to IL-12 ratio ($p < 0.01$). The ESR levels did not differ between the study group (50 vs. 42 $p = 0.16$), while the IL-12 values were lower in the infection group (10.6 pg/mL vs. 71.6 pg/mL, $p = 0.007$). The tumor load did not influence any of the studied infection markers within the study groups.

For identifying bacteremia by area under the operating characteristics curves (AUC), the highest values were obtained for PCT (0.92) and neopterin (0.90), and slightly lower values were recorded for the ratios neopterin to IL-12 (0.79) and IL-10 to IL-12 (0.75). None of the markers or ratios were good for differentiating non-bacteremic infections from neoplastic fever, the AUC values rangin from 0.27 for ESR to 0.61 for IL-10 to IL-12 ratio. The simultaneous use of the ratio of neopterin to IL-12 with its high sensitivity (82%) and that of IL-10 to IL-12 with its high specificity (90%) should be further studied.

Keywords: neoplasms, bacterial infection, neoplastic fever, cytokines.

To make a prairie it takes a clover and one bee,
One clover, and a bee,
And revery.
The revery alone will do.
If bees are few.

Emily Dickinson 1830–1886

To my sons Elias and Juhana

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Abbreviations

APP	acute-phase protein
APR	acute-phase response
AUC	area under receiver operating characteristic curve
CI	confidence interval
CRP	C-reactive protein
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
INF	interferon
IL	interleukin
IL-1r	IL-1 receptor
IL-1ra	IL-1r antagonist
LPS	lipopolysaccharide
MCH	major histocompatibility complex
MMP	matrix metalloproteinase
mAb	monoclonal antibody
MIP	myeloid progenitor inhibitor
NK cells	natural killer cells
NPV	negative predictive value
NHL	Non-Hodgkin lymphoma
PPV	positive predictive value
PCT	procalcitonin
ROC	receiver operating characteristic curve
Th1	T helper 1 lymphocyte
Th2	T helper 2 lymphocyte
TNF	tumor necrosis factor
TGF	transforming growth factor

List of original articles

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Kallio R, Bloigu A, Surcel H-M & Syrjälä H (2000) C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumours and lymphomas. Support Care Cancer, in press.

II Kallio R, Surcel H-M, Bloigu A & Syrjälä H (2000) C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients. Eur J Cancer 36: 889–894.

III Kallio R, Surcel H-M, Bloigu A & Syrjälä H Admission neopterin and interleukin-12 concentrations in identyfying infections in adult cancer patients. Cytokine, submitted for publication.

IV Kallio R, Surcel H-M, Bloigu A & Syrjälä H Balance between interleukin-10 and interleukin-12 in adult cancer patients with and without infections. Eur J Cancer, submitted for publication.

Contents

1 Introduction

The increasingly intensive chemotherapeutic treatment, the use of peripheral stem cell transplantation, the increasing use of central venous access devices and the antimicrobial prophylaxis have altered the epidemiology as well as the pattern of infections in cancer patients. Infections are the major cause of morbidity and mortality in patients with malignant diseases due to their several impairemnts of host defence (Zembower 1998). The number of studies on the impact of combined-modality therapy (surgery, irradiation, chemotherapy) on the infection rate is limited (Zembower 1998). It has been recently shown that the cause of fever in febrile neutropenic cancer patients is microbiologically defined infection in 44% (of which cases 80% are bacteremic), clinically defined infection in 17% and unknown in 39% (De Pauw *et al.* 1994). It has been estimated that 75% of all deaths in acute leukemia are attributable to infection (Bjeknes *et al.* 1999), while the corresponding figure in patients with solid tumors is 50% (Browder *et al.* 1961, Notter *et al.* 1980)**.**

The differential diagnosis of infections 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. Thus, the use different markers in terms of diagnosing infection in cancer patients is limited and not quite reliable.

These diagnostic difficulties lead to long periods of hospitalization and empiric antimicrobial therapies, which are expensive and impair the patient's quality of life. Unnecessary empiric antimicrobial treatments also increase the risk of developing resistant bacterial strains. Therefore, better diagnostic methods are needed for the diagnosis of infections in adult cancer patients.

2 Review of the literature

2.1 History and background

The differential diagnosis between neoplastic fever and infection in cancer patients has fascinated investigators for decades. In the studies published since the 1950s, the prevalence of neoplastic fever has varied from 5.4% to 56% (Boggs & Frei 1960, Silberman *et al.* 1965, Bodey *et al.* 1978, Chang & Gross 1984, Johnson 1996), probably reflecting both the knowledge and the diagnostic methods available in the different decades. Because neutropenic infection has been the most common cause of death in cancer patients, a large number of studies have focused on the diagnosis and management of neutropenic infections in pediatric and adult cancer patients (Mackie *et al.* 1979, Rose *et al.* 1981, Peltola *et al.* 1983, Peltola & Holmberg 1983, Starke *et al.* 1984, Rintala *et al.* 1992, Katz *et al.* 1992, Riikonen *et al.* 1993, Santolaya *et al.* 1994, Manian 1995, Kinnunen *et al.* 1996, Gillespie & Masterton 1998, Lyytikainen *et al.* 1998). Along with the findings concerning more effective antileukaemic chemotherapies, the knowledge and methods for the diagnosis of severe treatment-related infections have also improved and led to generally accepted guidelines for diagnosis and empiric antimirobial therapy of neutropenic cancer patients (Pizzo 1999). Recently, the major interest in such studies has focused whether the empiric antimicrobial therapy given to neutropenic patients with infections should be monotherapy or combined antimicrobial therapy (Raad *et al.* 1998a, Ramphal 1999, Vandercam *et al.* 2000) or on the timing and prophylaxis of antifungal therapy (Bohme *et al.* 1999, Johansen & Gotzsche 1999, Nucci *et al.* 2000)**.** In addition, attempts have been made to categorize the patients into low-risk patients with ambulatory treatment and high-risk patients with prompt hospitalization and broad-spectrum antimiocrobial therapy (Raad *et al.* 1998b, de Bont *et al.* 1999, Minotti *et al.* 1999).

The infection problems encountered in patients with solid tumors differ from those of neutropenic patients. Although treatment schedules do not usually result in long-term or profound neutropenia, tumor invasion and disruption of anatomic barriers (tumors of skin, oral cavity, nasopharynx, and gastrointestinal, respiratory and urogenital tracts), for example, predispose patients with solid tumors to infections. In addition, patients with primary or metastatic tumors in the central nervous system are also at risk for infections. As a consequence of neurologic deficiencies, the impaired gag reflex exposes them to

aspiration pnemonia and impaired micturition may cause recurrent urinary tract infections. Besides, metastatic bone marrow infiltrates may result in neutropenia in carcinomas of the breast, lung, kidney, adrenal, and thyroidea (Zembower 1998).

The wide spectrum of cancer treatments and their combinations available increase the risk of treatment-associated infections. Repeated, long-lasting chemotherapy schedules require central venous catheters, exposing the patients to transfusion and catheter-related intravascular infections (Raad 2000). Radiation as well as diagnostic and invasive procedures also predispose patients to infections (Glauser & Zinner 1982).

As described above, the diagnosis and treatment of neutropenic infections in patients with malignancies is well established (Pizzo 1999). However, it is important to realize that non-neutropenic infections constitute an increasingly common clinical problem in oncology wards. The practical experience of the management of neutropenic infections cannot be directly adapted to non-neutropenic conditions, and the methods which have proved sufficiently sensitive and specific in the case of severe neutropenic infections are not necessarily applicable to detecting non-neutropenic infections. Moreover, a current textbook of oncology seems to underestimate both the importance and the treatment of non-neutropenic infections in cancer patients (Freifeld *et al.* 1997).

2.2 Acute-phase response

The complex series of reactions initiated in response to infection, physical trauma, or malignancy is called the acute-phase response (APR). These reactions aim to prevent ongoing tissue damage, isolate and destroy the infective organism and activate the repair processes necessary to restore the host/organism's normal function (Baumann & Gauldie 1994). APR is characterized by leukocytosis, fever, alterations in the metabolism of many organs as well as changes in the plasma concentrations of various acute-phase proteins (APPs) (Hack *et al.* 1997b, Gabay & Kushner 1999). APPs have been defined as any protein whose plasma concentrations increases (positive acute-phase proteins; fibrinogen, serum amyloid A, albumin, C-reactive protein) or decreases (negative acute-phase proteins; albumin, transferrin, insulin growth factor I) by at least 25 percent during an inflammatory disorder (Morley & Kushner 1982). The main stimulators of APP production are the inflammation-associated cytokines, which are produced during inflammatory processes and participate in it: interleukin(IL)-6, IL-1β, tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), transforming growth factor β (TGF-β) and possibly IL-8 (Kushner 1993, Wigmore *et al.* 1997, Gabay & Kushner 1999). The local inflammation in both cancer and infection is accomppanied by APR upon activation by cytokines (Cavaillon & Duff 1999).

2.3 Cytokines

Cytokines are soluble mediators secreted by many cell types after a large panel of stimuli. They significantly regulate and determine the nature of the immune response by promoting survival, proliferation, differentiation, activation of cells or cell death. Cytokines mostly act locally in an autocrine or paracrine manner, but some of them, including IL-12, also exert systemic effects. They act at very low concentrations (μg/ml and pg/ml), and to achieve a maximal biological effect, only a fraction of their receptors are required to be occupied. Different cytokines can induce similar biological activities in their target cells. Cytokine interactions can be synergistic, inhibitory or modulating. Many cytokines have been cloned, sequenced and characterized, which has further promoted cytokine research. The nomenclature has been changed from a descriptive system based on biological action to a rational system with sequential numbering (e.g. endogenous pyrogen to IL-1). Cytokine functions are regulated in multiple ways: at the levels of both the producer cell (by means of transcriptional, translational and post-translational regulation) and the target cell (the accessibility of the specific receptor or its signal transduction can be modulated). The binding capacity of a cytokine can be modified in many ways: by decreasing the number or affinity of its receptors, receptor antagonists, non-receptor binding proteins, anti-cytokine autoantibodies and soluble cytokine receptors. (Dy *et al.* 1999).

An inflammatory process leads to the activation of the cytokine network. In the early phase of this process, proinflammatory cytokines (TNF-α, IL-1β, INF-γ and IL-12 are released. The activity of proinflammatory cytokines is counteracted by the production of anti-inflammatory cytokines (IL-4, IL-10, IL-13 and TGF-β) and soluble inhibitors of proinflammatory cytokines (soluble TNF-α receptor, soluble IL-1 receptor, and IL-1 receptor antagonist) (Cavaillon & Duff 1999, van der Poll & van Deventer 1999, Golab 2000).

In cancer, there is evidence that inflammation plays an essential role at each stage of the disease (initiation and proliferation), and both tumor and inflammatory cells are able to directly or indirectly either inhibit or stimulate tumor growth (Seung 1999). The effectiveness of tumor development has been demonstrated to correlate directly with the degree of the inflammatory reactions, and it seems that there are interactions between the cytokines produced in response to inflammatory reactions and tumor growth and even indications that inflammatory cytokines favor tumor promotion (Seung 1999, Fidler 2000).

Thus, the key point in the influence of cytokines on both cancer and infection is the balance between the proinflammatory and anti-inflammatory cytokines, i.e., for example, in cancer the balance between between IL-10 and IL-12 and in the infection the balance between IL-10 and TNF-α (van Dissel *et al.* 1998, Parmiani *et al.* 1999).

2.4 Th1/Th2 differentiation

During infection, T and B lymphocytes recognize microbes by means of antigen-specific cell-surface receptors. The humoral immune response is mediated by B cells and the antibodies they produce.

T lymphocyte response to antigenic challenges is called the cellular immune response. T lymphocytes can be categorized and functionally divided into CD4+ (T helper lymphocytes) cells and CD8+ (cytotoxic T lymphocytes) by the type of antigen receptors and a small number of accessory markers on their cell surface. T cells can be further differentiated into T helper 1 and T helper 2 cells (Salgame *et al.* 1991). The presence of IL-12 (produced by phagocytic cells) at the time of T cell priming drives to Th1 differentiation and that of IL-4 (produced by subsets of T cells and mast cells) to Th2 differentation (Hsieh *et al.* 1993**,** Dy *et al.* 1999, Johnson & Brown 2000). Th1 cells produce proinflammatory cytokines (INF-γ and IL-2) and are responsible for phagocyte-dependent protective host responses. Th2 cells secrete anti-inflammatory cytokines (IL-4, IL-10, IL-13 and TGF-β) and IL-5 and have been considered responsible for the phagocyte-independent protective host responses (Dy *et al.* 1999, Romagnani 2000)**.**

The Th1/Th2 paradigm has been further strengthened by *in vitro* and *in vivo* data showing an antagonism between Th1 and Th2 lymphokines. IL-4 promotes Th2 development and antagonizes Th1 development, whereas INF-γ and IL-12 promote Th1 development and antagonize Th2 development (Johnson & Brown 2000).

2.5 Markers for identifying infections

In this study the most widely and routinelly used ESR and CRP has been considered as traditional markers of infection and the other ones as new markers.

2.5.1 Erythrocyte sedimentation rate (ESR)

The erythrocyte sedimentation rate (ESR) is a quick, simple and inexpensive laboratory test that has been used routinely for over 80 years (Westergren 1924, Bedell & Bush 1985) to measure the height of the layer of red blood cells that settle in a tube of anticoagulated blood in a specific unit of time, most commonly an hour. The usefulness of ERS in various diseases has been widely studied, and the highest ESR levels have been found in association with infections, collagen vascular diseases and metastatic malignancies (Payman 1962, Sox & Liang 1986, Dinant *et al.* 1995, Brigden 1998, Bridgen 1999). According to a recent study, the accelerated sedimentation rate in the above mentioned conditions is caused by increased concentrations of APPs; actually, the observed ESR level reflects the concentrations of several plasma proteins (Ruhenstroth-Bauer *et al.* 1990).

These plasma proteins vary in different conditions, including malignancies and infections. In anemia, for example, the decreased concentration of red blood cells speeds up the sedimentation rate, thereby raising the ESR level (Brigden 1998).

Cancer patients have been commonly thought to have elevated ESR levels, which has been suggested to indicate metastatic carcinoma (Coggins 1983). However, it was already noted 40 years ago that ERS rates greater than 100 did not differentiate between patients with or without metastatic disease (Payman 1962). The clinical diagnoses associated with an ESR of 100 mm/h or more made in different studies indicated that infection was the most common reason for the elevation (33%–60%), while the malignant disease accounted for only 14–17% of the instances (Wyler 1977, Ford *et al.* 1979, Fincher & Page 1986).

ESR has been found to be a prognostic and predictive marker correlating with disease activity as well as survival in different types of malignancy, such as renal cell carcinoma, prostatic cancer, adult and pediatric Hodgkin´s disease and Non-Hodgkin lymphoma (NHL), gastric carcinoma, breast carcinoma and colorectal carcinoma (Thynne 1979, Thynne & Greening 1980, Child *et al.* 1980, Margerison & Mann 1985, Sox & Liang 1986, Janssen *et al.* 1987, Imai *et al.* 1990**,** Henry-Amar *et al.* 1991, Johansson *et al.* 1992, Ljungberg *et al.* 1997, Brigden 1998).

ESR has been routinely used for decades as a non-specific marker in the diagnosis of infections (Sox & Liang 1986, Stuart & Whicher 1988, Thoren & Wigren 1991, Miettinen *et al.* 1993, Brigden 1998, Gabay & Kushner 1999). However, the diagnostic use of ESR has been generally replaced by the measurement of C-reactive protein (CRP), which changes faster (Hansson & Lindquist 1997, Gabay & Kushner 1999).

There are very few studies concerning ESR as an infection marker in non-neutropenic cancer patients. However, a recent study showed the ESR level to be higher in patients with postoperative intracranial abscesses than the in early recurrence of malignant glioma (Vogelsang *et al.* 1998).

2.5.2 C-reactive protein (CRP)

CRP is the most widely analysed APP in clinical practice (Hansson & Lindquist 1997). It belongs to the pentraxin family of proteins with a structure of five identical, non-covalently bound subunits arranged in cyclic symmetry. It was recognized by its ability to precipitate the C-polysaccharide of pneumococci (Kushner 1982). The production of CRP in the liver is stimulated by IL-1, IL-6, TNF-α and TGF-β (Dinarello 1984, Baumann & Gauldie 1990, Lee *et al.* 2000). The major function of CRP by binding phosphocholine is to regonize some foreign pathogens and phospholipid constituents in damaged cells (Volanakis 1997). It also activates the complement system and contributes to the induction of inflammatory cytokines and tissue factors in monocytes (Ballou & Kushner 1992, Cermak *et al.* 1993, Volanakis 1997).

According to some earlier studies of progressive malignant diseases, alterations in CRP levels have been published with controversial results in terms of the tumor load (Boggs & Frei 1960, Child *et al.* 1980, Morley & Kushner 1982, Pepys & Baltz 1983,

Peltola *et al*. 1983, Weinstein *et al*. 1984, Nel *et al*. 1985, Fearon *et al*. 1991, Falconer *et al*. 1995, Scott *et al*. 1996, Fearon *et al*. 1998). CRP has been found to be prognostic in, for example, epithelial ovarian carcinoma, metastatic renal cell carcinoma, advanced pancreatic cancer, colorectal cancer and NHL, pancreatic cancer and non-small-cell lung cancer, where elevated pretreatment and follow-up serum levels have predicted a poor outcome (Blay *et al*. 1992, Falconer *et al*. 1995, Scott *et al*. 1996, Legouffe *et al*. 1998, Nozoe *et al*. 1998, Barber *et al*. 1999, Fujikawa *et al*. 1999, Kodama *et al*. 1999). In breast cancer, however, CRP was neither prognostic nor predictive (Heys *et al*. 1998).

Patients with cytotoxic treatment have been shown to have slightly increased values of CRP, presumably due to tumor degradation (Milroy *et al.* 1989, Staal-van den Brekel *et al.* 1997, Senderowicz *et al.* 1998).

The determination of CRP has been used for years in the diagnosis of infection as well as to monitor the outcome of infection treatment in patients with haematological and pediatric malignancies with profound neutropenia (Mackie *et al*. 1979, Rose *et al*. 1981, Gozzard *et al*. 1985, Grutzmeier & von Schenck 1986, Katz *et al*. 1992, Riikonen *et al*. 1993, Rintala 1994, Santolaya *et al*. 1994, Manian 1995, Kinnunen *et al.* 1996, Engel *et al.* 1998, Lyytikainen *et al*. 1998, Lehrnbecher *et al.* 1999). Serial measurements of serum CRP levels have been shown to be helpful in determining the risk for unidentified infections or poor outcome in neutropenic cancer patients, whenever this marker has remained high for days, as well as for the evaluation of the response to antibiotic treatment in patients with severe bacterial infections and for identifying postoperative infections (Santolaya *et al*. 1994, Manian 1995, Rintala *et al.* 1995, Hansson & Lindquist 1997). The CRP level typically exceeds 100 mg/l in patients with bacteremia, and a stable or increasing CRP level after the first 3–4 days of the initiation of treatment usually indicates a treatment failure (Hansson & Lindquist 1997).

There are only a few studies concerning CRP as a marker of infection in patients with solid tumors and non-neutropenic infections. In a study of the plasma neopterin-to-CRP ratio, the mean value of CRP was higher in the infection group (125 g/l) than in the cancer cachexia group (34 g/l) (Iwagaki *et al.* 1995b*).*

2.5.3 Procalcitonin (PCT)

Procalcitonin (PCT) is a 116 amino acid propeptide of calcitonin, which is normally produced by C-cells of the thyroid gland. The reason for increased PCT secretion in patients with severe infections has remained unknown (Karzai *et al.* 1997). According to a very recent *in vivo* and *in vitro* study, the major source of PCT seemed to be the liver, and PCT may thus be considered an acute phase protein (Nijsten *et al*. 2000). In this study, its production was induced by recombinant human TNF-α and recombinant human IL-6 (Nijsten *et al*. 2000). After an injection of endotoxins, the PCT concentration starts to increase within 3 to 6 hours and reaches a plateau in 12 hours (Brunkhorst *et al.* 1998).

Enhanced production of calcitonin-like peptides or calcitonin precursor peptides has been seen in patients with medullary carcinoma of thyreoidea, tumors of the neuroendocrine system and hepatocellular carcinomas (Ghillani *et al*. 1989). The

proportion of positive PCT findings in the sera of patients with different types of malignancy (thyroid adenocarcinoma, testicular tumor, prostatic cancer, melanoma, ovarian carcinoma, Ewing sarcoma, gastrointestinal and pancreatic adenocarcinoma, leukemia, myeloma, breast cancer) has varied from 7% in breast cancer to 62% in hepatocellular carcinoma and appears to depend on cell type and tumor stage (Ghillani *et al*. 1989**).**

PCT has been reported to be superior in differentiating infectious from non-infectious causes of inflammation (Karzai *et al*. 1997). It has been proposed as a new diagnostic marker in various severe infections (al-Nawas & Shah 1996, Karzai *et al.* 1997), such as septic shock (de Werra *et al.* 1997, Brunkhorst *et al*. 1998, Whang *et al.* 1998), bacterial meningitis (Gendrel *et al.* 1997) and neonatal infections (Assicot *et al.* 1993, Monneret *et al.* 1997). In addition, PCT has emerged as a promising indicator and a powerful predictor of bacteraemia even in neutropenic patients with hematological malignancies (Bernard *et al.* 1998, Lestin *et al*. 1998**,** Engel *et al.* 1999, Ruokonen *et al.* 1999). In a recent study, the specificity of PCT in differentiating bacteremia from non-bacteremia in neutropenic patients was high (88%), but its sensitivity remained low (55%). In that study, PCT concentrations seemed to be low in gram-positive bacteremia (Ruokonen *et al.* 1999).

2.5.4 Neopterin

Neopterin is a pteridine intermediate metabolite in the biopterin synthetic pathway, and it is synthesized and secreted by activated monocytes and macrophages (Sheldon *et al*. 1991, Iwagaki et al. 1995b). According to *in vitro* studies, the secretion of neopterin is induced by INF-γ (Romagnani 1994, Lucey *et al.* 1996). *In vitro* studies have also shown that neopterin is able to enhance the release of TNF-α from lipopolysaccharide-stimulated monocytes, thus suggesting an ability of neopterin to modulate the cytokine profile subsequent to immune activation (Barak & Gruener 1991, Fuchs *et al.* 1992). It has also been suggested that neopterin may act as an endogenous inhibitor of folate synthesis by intracellular micro-organisms (Hamerlinck 1999)**.** Increased neopterin concentrations have been found in a large variety of conditions in which the cell-mediated immune system is activated, such as organ and bone marrow transplantation, rheumatoid arthritis, systemic lupus erythematosus, autoimmune diseases, inflammatory bowel diseases, multiple sclerosis, sarcoidosis, diabetes, congestive heart failure and infectious diseases (Reibnegger *et al.* 1986a, Sheldon *et al.* 1991, Fuchs *et al*. 1992, Iwagaki *et al.* 1995a, Muller *et al.* 1998b, Hamerlinck 1999).

In malignancies, increasing follow-up neopterin concentrations in serum, urine or ascitic fluid have been found to indicate an enhanced risk of tumor relapse, metastases or death (Fuchs *et al*. 1992, Murr *et al.* 1999b). Neopterin concentrations have been found to be elevated in patients with different types of malignancy: in Non-Hodgkin lymphomas, in chronic lymphoblastoid leukemia, in Hodgkin´s disease, and in multiple myeloma (Hausen *et al.* 1982, Abate *et al.* 1989) in gynecological malignancies (Reibnegger *et al.* 1986b, Reibnegger *et al.* 1987) in tumors of the male genitourinary tract (Aulitzky *et al.* 1985, Lewenhaupt *et al.* 1986) in lung cancer (Fuchs *et al*. 1992), and in squamous-cell

carcinomas of the oral cavity (Murr *et al*. 1998). Most malignancies, with the exception of breast cancer and gastrointestinal cancer, show a striking dependence of neopterin levels on the stage of the malignancy as well as an association with the prognosis. In the latter types of cancer, less than half of patients had elevated neopterin levels without correlation with the tumor stage (Fuchs *et al*. 1992, Putzki *et al.* 1987). Altough only 20% of breast cancer patients had raised neopterin levels (Fuchs *et al.* 1992) in a recent study, neopterin concentration still correlated with the presence of distant metastases and even with tumor differentiation (Murr *et al.* 1999a).

Neopterin has been recognized as a valid marker of cellular immune activation, and it has therefore been investigated as a possible predictive marker for supportive immunotherapy as well as for the evaluation of the response to immunotherapy in, for example, pancreatic cancer and renal cell carcinoma (Birk *et al.* 1999, Fumagalli *et al*. 1999). In a group of stage III melanoma patients, the elevation of neopterin concentration did not differ during the therapy between patients with a major response and non-major responders (Anderson *et al.* 1998).

Increased neopterin secretion typically occurs during acute viral infections, intracellular and extracellular bacterial infections, as well as in parasitic infections (Fuchs *et al.* 1984, Prior *et al.* 1987, Reibnegger *et al.* 1988, Fuchs *et al*. 1992). High neopterin concentrations have been shown to be prognostic and predictive in septic patients with or without trauma (Strohmaier *et al.* 1987) and also in patients with HIV infection (Fuchs *et al*. 1992, Hutterer *et al.* 1992).

The role of neopterin in cancer patients with infection has been rarely investigated. In a recent study, neopterin was found to be a promising alternative to distinguish bacterial infection from fever of unknown origin within eight hours of the onset of fever in neutropenic patients with hematologic malignancy (Ruokonen *et al*. 1999).

2.5.5 Interleukin-8 (IL-8)

The migration of leukocytes from blood vessels to an inflammatory site requires chemotactic factors, which are produced locally at the site of inflammation. In the last decade, at least two superfamilies of structurally related cytokines showing chemotactic activity for specific types of leukocytes have been identified: the C-C chemokine superfamily and the C-X-C superfamily. (Adams & Lloyd 1997, Hack *et al.* 1997a, Wuyts *et al*. 1999). IL-8 (8-9 kDa), which belongs to the latter group, is an important chemotactic regulator of neutrophil function *in vivo* (Baggiolini *et al.* 1989, Baggiolini *et al.* 1994, Hack *et al*. 1997a, Tedla *et al.* 1999).

IL-8 is produced by mononuclear cells, by other leukocyte cell types (myeloid precursors, natural killer (NK) cells, neutrophils, eosinophils, mast cells), various tissue cells (e.g. fibroblasts, endothelial cells, epithelial cells) and tumor cells (Wuyts *et al*. 1999). IL-8 production is induced by a variety of stimuli, such as cytokines and bacterial and viral products (Wuyts *et al*. 1999). During febrile episodes and neutropenia,

neutrophils and monocytes are unlikely to be the main source of IL-8 (Ostermann *et al.* 1994), and such agents as TNF-α or endotoxin have been shown to stimulate IL-8 production from endothelial cells (Huber *et al.* 1991, von Asmuth *et al.* 1993).

The onset of angiogenesis requires a change in the local equilibrium between the proangiogenetic and antiangiogenetic regulators produced by tumor cells, stromal cells and infiltrating leukocytes. In normal tissue, inhibiting factors of angiogenesis predominate, while in rapidly dividing tissues, the balance between angiogenetic factors favors process stimulation (Adams & Lloyd 1997, Hack *et al.* 1997a, Wuyts *et al.* 1999). IL-8 is one of the angiogenic molecules that has been found to induce neovascularization (Fidler 2000). Recent studies suggest that a distruption of the balance between angiogenic molecules should allow the design of potent antiangiogenic therapies against primary and metastatic cancer (Fidler 2000**,** Fujisawa *et al.* 2000). IL-8 is also mitogenic and, within a neoplasm, it is secreted by inflammatory and neoplastic cells (Inoue *et al.* 2000a, Inoue *et al.* 2000b).

IL-8 concentration increases during different infections, such as bacteremia (Hack *et al.* 1992, Hynninen *et al.* 1997) and meningococcal disease (Halstensen *et al* 1993). In neutropenic patients, enhanced IL-8 production has been demonstrated comparable to PCT in predicting bacteremia (Engel *et al.* 1999). After chemotherapy, IL-8 has been found promising as an early diagnostic marker in monitoring neutropenic patients for forthcoming fever: IL-8 levels were elevated three days, IL-6 two days and CRP one day before the onset of fever (Lindemann *et al.* 1995). In a recent study concerning patients with acute lymphoblastic or myeloid leukaemia, IL-8 was found to be increased significantly more often in patients with chemoterapy-related neutropenia and fever due to bacteraemia than in neutropenic patients with fever of non-bacterial origin (de Bont *et al.* 1999). This approach may warrant the early discharge of a defined group of neutropenic patients with fever who are at low risk for septicaemia. High IL-8 has been shown to predict organ failure in community-aquired septic shock (Takala *et al.* 1999b) and a poor outcome in postoperative multi-organ failure (Hamano *et al.* 1998) and nosocomial bacterial infections in neonates (Franz *et al.* 1999a)**.**

2.5.6 Interleukin-10 (IL-10)

IL-10 (18.5 kDa) has a pivotal role in the regulation of responses in cell-mediated immunity. The major sources of IL-10 are mononuclear phagocytes, CD4+T lymphocytes, B cells, and keratinocytes (Johnson & Brown 2000). Tumor cells also produce IL-10 (Pretolani *et al.* 1999). The mechanisms of regulation of IL-10 production in monocytes are poorly understood at cellular and biochemical levels (Brennan & Feldmann 2000). The production of IL-10 is induced by many microbes, several cytokines (TNF-α, IL-6, IL-12) and hormones (glucocorticoids, epinephrine). IL-10 has also been shown to have an autoregulative feedback mechanism (Pretolani *et al.* 1999).

IL-10 has been called an immunosuppressive cytokine, because it deactivates macrophages and inhibits both the induction and the effector phases of T cell responses . IL-10 inhibits the antigen-presenting cell function of monocytes/macrophages by down-

regulating their expression of MHC class II and co-stimulatory molecules, including co-factor B7 and intercellular adhesion molecule-1 (de Waal Malefyt *et al.* 1991, Pretolani *et al*. 1999). Furthermore, IL-10 inhibits the synthesis of IL-12 by the antigen-presenting cells. The anti-inflammatory function of IL-10 is mediated by the inhibition of proinflammatory cytokine production, such as IL-1α, IL-1β, IL-6, IL-8, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemokines, including MIP-1a, and by promotion of the release of the IL-1 receptor antagonist. IL-10 also prevents the release of oxygen free radicals and the nitric oxide-dependent microbicidal activity of macrophages and neutrophils as well as lowers their ability to generate prostaglandins (Oppenheim & Fujiwara 1996, Pretolani *et al*. 1999).

In comparison with healthy controls, patients with different types of cancer have been found to have increased serum levels of IL-10 correlating with the extent of the disease (Fortis *et al.* 1996, Avradopoulos *et al.* 1997, De Vita *et al.* 1999, Wojciechowska-Lacka *et al*. 1999). In addition, increased IL-10 seems to be prognostic in patients with intermediate or high grades of NHL with higher IL-10 levels at the time of diagnosis than seen in patients with low grades of NHL. Furthermore, multivariate analysis showed IL-10 to be an independent prognostic factor with a significant inverse correlation with both shorter overall and progression-free survival (Blay *et al.* 1993). These observations are in harmony with the studies suggesting that IL-10 provides better conditions for tumor growth (Fujieda *et al.* 1999, Kazuyuki *et al.* 1993).

Elevated IL-10 levels are also associated with different types of infection, such as meningococcal septic shock (van Deuren *et al.* 1994), gram-positive and gram-negative bacteremias (Marchant *et al.* 1994), malaria (Watier *et al.* 1993), hepatitis C (Cacciarelli *et al*. 1996) and fungal infections (Vecchiarelli *et al*. 1996). High IL-10 serum concentrations have been especially linked with the severity of subsequent complications (Friedman *et al.* 1997) and even mortality in febrile patients and severe sepsis (van Dissel *et al.* 1998, Gogos *et al.* 2000).

2.5.7 Interleukin-12 (IL-12)

Although IL-12 was originally discovered as a product of Epstein-Barr virus -transformed B-cell lines, subsequent studies have suggested that the major source of IL-12 consists of monocytes, macrophages and B lymphocytes (Johnson & Brown 2000). IL-12 (70 kDa glycoprotein) is a multifunctional proinflammatory cytokine with pleiotrophic effects; it activates NK and T cells to produce several cytokines, especially INF-γ. In addition, it enhances the cytotoxic activation of activated NK cells and favors the generation of cytolytic T cells (Hensler *et al*. 1998a). IL-12 also enhances the phagocytic and bacteriocidal activity of phagocytic cells and their ability to release pro-inflammatory cytokines, including itself. IL-12 is the key immunoregulator molecule favoring the differentiation and function of Th 1 cells (see chapter 2.4) and inhibiting the differentiation of Th 2 cells (Trinchieri 1999).

Overproduction of IL-12 is potentially dangerous, if uncontrolled, and there are therefore several downregulation mechamisms to avoid this: Transformations of growth factor beta (TGF-β), IL-4, IL-10 and IL-13 inhibit and suppress the production of IL-12 (Trinchieri 1999). IL-12 also has an autoregulative feedback mechanism, as was recently shown in an experimental study of renal cell carcinoma, where long-term administration of IL-12 decreased its own serum levels (Rakhit *et al.* 1999).

In cancer patients, the antitumor effect of IL-12 is based on several mechanism: The activation of innate and antigen-specific adaptive immunity against tumor cells and the ability to inhibit tumor angiogenesis through INF-γ (Trinchieri 1999). The immunological properties of IL-12 make it a candidate adjuvant for vaccination against cancer and infectious diseases. In fact, phase 1 and 2 clinical trials to evaluate the use of IL-12 in anticancer therapy have been initiated (Brunda & Gately 1995, Bajetta *et al.* 1998, Cavallo *et al.* 1999**,** Robertson *et al.* 1999b, Rodolfo & Colombo 1999, Portielje *et al.* 1999, Haicheur *et al.* 2000). However, systemic use of IL-12 *in vivo* seems to be toxic, and the clinical trial applications therefore focus on local (Rodolfo & Colombo 1999) and intermittent administration (Portielje *et al.* 1999).

The antitumor activity of IL-12 has been demonstrated in several *in vitro* studies and in animal models (Brunda *et al.* 1993, Hiscox *et al.* 1995, Siders *et al.* 1998, Dow *et al.* 1999, Dunussi-Joannopoulos *et al.* 1999, Hirschowitz *et al.* 1999, Mazzolini *et al.* 1999). As immunotherapy and chemotherapy may target different tumor escape mechanisms, their combinations have been suggested to be beneficial in the treatment of certain tumor types, as already observed in animal models with melanoma and leukemia cells treated with a combination of IL-12 and paclitaxel and IL-12 and doxorubicin/mitoxantrone (Zagozdzon *et al.* 1999, Golab *et al.* 2000).

IL-12 is also known as an endogenous inhibitor of angiogenesis, and the recent studies have been evaluated for such factors as the balance between the pro-angiogenetic factors thymidine phosphorylase and the vascular endothelial growth factor and IL-12 in human breast carcinoma (Toi *et al.* 1999). Moreover, intratumor injection of an adenoviral vector with IL-12 has been suggested to have anti-angiogenic effects enhancing the local and anti-tumor effects of irradiation (Seetharam *et al.* 1999).

IL-12 is crucial in the early phase of host defense against microbial infections, especially bacteria, fungi and intracellular parasites (Romani *et al.* 1997, Hensler *et al.* 1998b, Trinchieri 1999, van der Poll & van Deventer 1999). It is produced within a few hours of infection (Trinchieri 1999). Elevated IL-12 levels have been demonstrated in *Legionella* pneumonia (Tateda *et al.* 1998). Actually, IL-12 administration has been shown to markedly increase survival after sepsis in the mouse burn model (O´Suilleabhain *et al.* 1996, Goebel *et al.* 2000). Contrary to this, the administration of IL-12 antiserum reduced survival despite regular antibiotic medication in a mouse model (Steinhauser *et al.* 1999). Studies on the diagnostic use of IL-12 in infections are thus far lacking.

2.5.8 The IL-10 to IL-12 ratio

Because of the opposite roles of IL-10 and IL-12 in the regulation of the cytokine network, the balance between these cyokines has attracted interest in various clinical instances, such as autoimmune diseases, allograft rejection, arthritis, atherosclerosis, gynecology and ophthalmology (Uyemura *et al.* 1996, Yin *et al.* 1997, Huang *et al.* 1998 Muller *et al.* 1998a, Akpek *et al.* 1999, Gao *et al.* 1999**,** Karussis *et al.* 1999a, Szereday *et al.* 1999). The balance between IL-10 and IL-12 has been studied also both in oncology (O'Donnell *et al.* 1999, Stolina *et al.* 2000) and in infections (Mokuno *et al.* 1999, Swaminathan *et al.* 1999). In an experimental pneumonia model, high IL-10 and low IL-12 mRNA levels exposed mice to *Klebsiella pneumonie* infection (Zisman *et al.* 1998)**.**

The balance between IL-10 and IL-12 can be utilized in treatment strategies including administration of IL-10 in, for example, various inflammatory and infectious diseases in humans (Opal *et al.* 1998). It may be useful in the treatment of septic shock due to gram-negative and gram-positive bacteria (Pajkrt *et al.* 1997). Recent studies have suggested that the administration of anti-IL-10 antibodies may be beneficial in preventing the development of injury-induced immune dysfunction and seems to improve survival in experimental polymicrobial sepsis (Song *et al.* 1999, Lyons *et al.* 1999). On the other hand, IL-12 has been used in oncology in the same manner (see pages 23).

2.6 Summary of literature

To summarize the literature review, there are plenty of publications on ESR, CRP, PCT, neopterin, IL-8, IL-10 and IL-12 in the evaluation of pathogenesis and prognosis in oncology. Most of these markers have also been used in the evaluation of neutropenic infections. However, studies concerning the utility of these markers in the diagnosis of infections in cancer patients with solid tumors are not available, unless noted earlier in corresponding sections.

3 Purpose of the present study

The purpose of the present study was

1. to evaluate the ways in which CRP, ESR, PCT, neopterin, IL-8, IL-10, and IL-12 differ between cancer patients with and without infection and the possible influence of tumor load on these parameters, and
2. to evaluate CRP, ESR, PCT, neopterin, IL-8, IL-10, IL-12 in differentiating infections from neoplastic fever.

4 Study subjects and methods

4.1 Patients

Between September 1996 and March 1998, 92 consecutive cancer patients suspected by the attending oncologist to have a clinical infection were enrolled into this prospective study at the Department of Oncology and Radiotherapy, Oulu University Hospital. A Karnofsky performance score higher than 40 was required (the patients which do not require permanent hospital care). Informed consent was obtained. Only one episode per patient was included. Of the 92 patients evaluated for possible infection, 56 had infection, 10 had neoplastic fever without infection and 26 had to be excluded because they did not meet the study criteria. In addition, the non-infection group included 26 chemotherapy-naive patients without any suspicion of infection.

4.1.1 Pretreatment evaluation

The pretreatment evaluation of the 92 study patients included a medical history, a physical examination, two blood cultures obtained from different sites for aerobic and anaerobic bacteria and fungi (BacT/Alert®, Organon Teknika Corporation, Durham, NC, USA), a bacterial culture of urine (n = 86) and chest X-rays (n = 88). Other radiological examinations were made individually if clinically indicated, including radiography of the paranasal sinuses (n = 69), ultrasonography (n = 19), computed tomography (n = 11) and magnetic resonance imaging (n = 3). After the inclusion of the patient into this study, treatment and follow-up were made as a matter of routine by the oncologists working on the ward. The patient data were retrospectively analyzed jointly by an oncologist (R.K.) and an infectious disease physician (H.S.) by using the definitions given below.

4.1.2 Infection group (I-IV)

The diagnosis of bacteremia was based on a symptomatic clinical infection and a positive blood culture. The diagnosis of urinary tract infection required both symptoms and significant growth of bacteria $10^{4–5}$ cfu / ml in urine culture. The diagnosis of pneumonia was based on both respiratory symptoms and a pneumonic infiltrate that disappeared during the antibiotic treatment while the patient recovered. For other foci, distinct radiological or microbiological documentation and recovery during the antimicrobial treatment were required. In addition, the patients who had a clinical picture of infection and showed a clear antibiotic response with abatement of fever and decreasing CRP values during the follow-up were considered to have had infection, although no foci of infection could be demonstrated.

4.1.3 Non-infection group

The non-infection group consisted of 10 patients with neoplastic fever, of whom eigth had not received chemotherapy previously (paper I–IV) and 26 chemotherapy-naive patients (paper II–IV).

The patients were considered to have neoplastic fever if they did not have any evidence of infection clinically or in the examinations performed. Moreover, they did not respond to empirical antibiotic treatments, but typically showed a response to steroids, anti-inflammatory analgesics or radiotherapy.

The chemotherapy-naive patients were 26 voluntary patients (15 males and 11 females) with a mean age of 60 years without clinical infection, who had been randomly selected before their first course of chemotherapy.

4.2 Methods

4.2.1 CRP and ESR

The following laboratory parameters were assessed in our hospital laboratory: CRP by an automated Technicon H1^{TM} system (Tarrytown, New York, USA) and ESR by the Westergren tube method (Westergren 1924).

4.2.2 PCT

The serum PCT concentrations were measured as duplicates using a chemoluminescent immunoassay kit (LUMItest PCT, B.R.A.H.M.S. Diagnostica GMBH, Berlin, Germany) with a lower detection limit of 0.1 ng/ml (Karzai *et al*. 1997).

4.2.3 Neopterin

Serum neopterin levels were measured as duplicates by a commercially available the enzyme-linked immunosorbent assay (ELISA) kit (Neopterin ELISA, IBL, Hamburg, Germany) with a lower detection limit of 4 nmol/l and a reference value < 10 nmol/l for healthy individuals.

4.2.4 Cytokines

Cytokine concentrations were determined as duplicates by ELISA method using commercially available ELISA kits for IL-8 and IL-12 (Duoset, Genzyme Diacnostics, Cambridge, USA) and for IL-10 (PeliKine Compact^{TM}, CLB, Amsterdam, Holland) according to the manufacturer's instructions. The lower detection limits for the tests were 15 pg/ml for IL-8, 3 pg/ml for IL-10 and 10 pg/ml for IL-12.

4.2.5 Statistical analysis

The statistical analysis was performed using SPSS software (SPSS Inc. Chicago, Illinois, US). The calculations for continuous variables were performed with the Mann-Whitney U-test and those for categorical variables with Pearson´s χ^2-test (or Fisher's exact test when appropriate). Wilcoxon's signed-ranks test was used to compare the repeated measurements of CRP. The diagnostic applicability of the studied parameters to identify infections was evaluated using receiver operating characteristic curves (ROC) and corresponding area under curve (AUC) values and their 95% confidence intervals (CI) (Metz 1978, Gardner & Altman 1989). The ROC curves have been calculated by plotting the sensitivity versus 1-specificity for each possible cut-off value and then joining the points. The corresponding AUC values were obtained by using the SPSS statistical software. The test is ideal if its AUC value is 1.0, while a value of 0.5 does not differ from that obtained by chance.

The optimal cut-off values for the studied parameters in identifying infections were determined using the Youden index based on sensitivity and specificity (Youden 1950).

5 Results

5.1 Patients

Table 1 shows the study populations covered in the papers I–IV. Twenty-six of the 92 patients with suspected infection did not meet the above criteria of infection or neoplastic fever, because they had simultaneous antibiotic and cancer treatments and therefore had to be excluded.

Table 1. Description of cancer patients in papers I–IV

Paper	Patients	N
I	patients with infection	56
	patients with neoplastic fever	10
II–IV	patients with infection	56
	patients with neoplastic fever	10
	chemotherpay-naive patients without infection	26

The final study population consisted of 56 patients with infection (35 males, 21 females, I–IV) and ten patients with neoplastic fever (6 males, 4 females, I–IV). Seven (11%) of the 66 patients with suspected infection had a leukocyte count lower than $1.0 10^9$/L. The median duration of symptoms was statistically shorter in the infection group than in the neoplastic fever group (one day vs. 21 days, $p < 0.001$). The 56 cancer patients had the following infections: eight had bacteraemia (three had *Staphylococcus aureus*, and one each *Eshcerichia coli*, *Pasteurella multocida*, *Clostridium bifermentans*, another gram-negative anaerobic rod and mixed bacteraemia) and fifteen had pneumonia. The other foci were as follows: seven cases of urinary tract infection, two cases of sinusitis, one case each of infection at the insertion site of a central venous catheter, cholangitis, perirectal abscess, mediastinitis, pulmonary tuberculosis, erysipelas and *Herpes zoster* infection. In addition, seventeen patients had a clinical infection and showed a clear antibiotic response.

Table 2 shows the essential data of the infection group (n = 56) and the non-infection group (n = 36), which consisted of the ten cases with neoplastic fever and 26 chemotherapy-naive cancer patients (lymphoma 27%, lung cancer 31%, breast cancer 12% other 12%). The demographic data and the type and stage of cancer, when included into the study, did not differ between the study groups.

Table 2. Demographic data and type and stage of underlying cancer in infection and non-infection groups of cancer patients

Variable	Infection group (n = 56)		Non-infection group (n = 36)			
			Total group		Neoplastic fever patients[a]	
	No.	%	No.	%	No.	%
Gender						
Male	35	62.5	23	64	6	60
Female	21	37.5	13	36	4	40
Mean age (SD)	57	(16)	57	(13)	61	(13)
Tumor type						
Lymphoma	23	41	11	31	2	20
Lung cancer	7	12.5	13	36	5	50
Breast cancer	6	11	3	8	1	10
Gastrointestinal cancer	7	12.5	3	8	1	10
Urinary tract cancer	4	7	1	3	1	10
Other cancer	9	16	5	14	0	0
Stage						
St I	4	7	0	0	0	0
St II	7	13	5	14	0	0
St III	12	23	9	25	1	10
St IV	30	57	22	61	9	90

[a] = The characteristics of ten patients with neoplastic fever in the non-infection group are separately noted

5.2 Studied parameters in cancer patients with and without infection

Table 3 shows the median concentrations of the studied parameters in the cancer patients with and without infection. The median CRP ($p < 0.001$), PCT($p < 0.001$), neopterin ($p < 0.001$), IL-8 ($p = 0.032$), and IL-10 ($p = 0.005$) levels were statistically higher in the infection group than in the non-infection group, while the median concentration of IL-12 was lower ($p = 0.007$). The ratios of neopterin to IL-12 ($p < 0.001$) and IL-10 to IL-12 ($p < 0.001$) were statistically higher in the infection group.

Table 3. Median levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), neopterin, interleukin-8 (IL-8), interleukin-10 (IL-10) interleukin-12 (IL-12), neopterin to IL-12 ratio and IL-10 to IL-12 ratio in infection and non-infection groups of cancer patients.

Parameter	Infection group (n = 56)		Non-infection group (n = 36)		*p*-value
	Median	IQR*	Median	IQR	
ESR	50	25–89	42	11–84	0.16
CRP	91	40–191	19	10–98	< 0.001
PCT	0.28	0.16–0.57	0.12	0.02–0.23	< 0.001
Neopterin	12.8	8.1–26.6	4.0	4.0–9.5	< 0.001
IL-8	27.7	12.4–86.3	16.9	6.2–47.3	0.032
IL-10	3.8	1.7–11.4	1.8	0.6–4.6	0.005
IL-12	10.6	0–55.9	71.6	0.7–104.4	0.007
Neopterin to IL-12 ratio	1.74	0.3–151.3	0.11	0.04–30.3	< 0.001
IL-10 to IL-12 ratio	0.4	0.06–4.23	0.05	0.02–0.31	< 0.001

* IQR = Interquartile range (25th to 75th percentile).

5.3 Influence of tumor load on the studied parameters

5.3.1 Within the study groups

The tumor load did not influence the concentrations of any of the studied infection markers within the two study groups (Table 4), although ESR tended to be higher in advanced disease within the non-infection group (p = 0.09).

Table 4. The influence of tumor load within the study groups erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), neopterin, interleukin-8 (IL-8), interleukin-10 (IL-10) interleukin-12 (IL-12), neopterin to IL-12 ratio (neopterin/IL-12) and IL-10 to IL-12 ratio (IL-10/IL-12) in 66 cancer patients with suspected infection of whom 56 with infection and 10 patients with neoplastic fever without infection.

Parameter	Infection group (n = 56)			Non-infection group (n = 36)		
	local	advanced	*p*-value	Local	Advanced	*p*-value
ESR	50.0	51	0.909	10.0	42.0	0.09
CRP	103	83.00	0.835	10.0	22	0.54
PCT	0.28	0.31	0.50	0.11	0.13	0.51
Neopterin	17.0	11.5	0.27	4.0	4.0	0.21
IL-8	39.0	26.6	0.71	10.5	19.3	0.51
IL-10	2,56	4.54	0.188	3.12	1.8	0.77
IL-12	25.21	15.8	0.98	51.0	71.6	0.60
Neopterin/ IL-12	1.07	1.69	0.80	0.15	0.11	0.93
IL-10 / IL-12	0.09	0.40	0.32	0.07	0.05	0.57

5.3.2 Between the infection and non-infection groups

As figure 1 shows, the differences between the infection and non-infection groups remained statistically significant after subdivision of the cases into local and advanced disease: CRP ($p < 0.05$ and $p < 0.001$) and neopterin ($p < 0.01$ and $p < 0.001$) and the following markers only in advanced disease: PCT ($p < 0.001$), IL-10 ($p < 0.05$), IL-12 ($p < 0.05$), neopterin to IL-12 ratio ($p < 0.01$) and IL-10 to IL-12 ratio ($p < 0.01$)

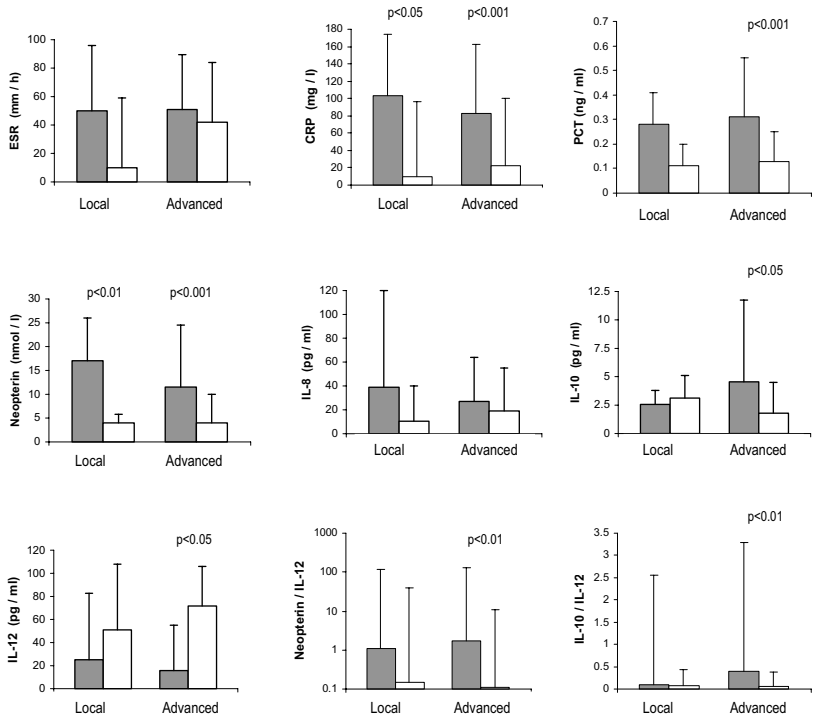

Fig. 1. Influence of the tumor load on the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin (IL)-8, IL-10 and IL-12 levels and on the ratios of neopterin to IL-12 and IL-10 to IL-12 in local (Stages I and II) and advanced (Stages III and IV) diseases in infection (filled column) and non-infection (open column) groups.

5.4 Discriminatory power of the the studied parameters in detecting infections in cancer patients

Discriminatory power was evaluated by three approaches using ROC curves and corresponding AUC values (table 5). Neopterin to IL-12 (0.64) and IL-10 to IL-12 (0.64) had the highest AUC values in differentiating infection in general from neoplastic fever. In discriminating bacteremia, the best AUC values were obtained for PCT (0.92) and neopterin (0.90). In discriminating non-bacteremic infections from neoplastic fever, the best, though relatively low, AUC values were obtained for the ratios of neopterin to IL-12 (0.60) and IL-10 to IL-12 (0.61).

Table 5. The area under curve (AUC) values for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), neopterin, interleukin-8 (IL-8), interleukin-10 (IL-10) interleukin-12 (IL-12), neopterin to IL-12 ratio (neopterin/IL-12) and IL-10 to IL-12 ratio (IL-10/ IL-12) in 66 cancer patients with suspected infection of whom 56 with infection and 10 patients with neoplastic fever without infection

Parameter	In general (56 versus 10)		Bacteremia (8 versus 58)		Non-bacteremic infections (48 versus 10)	
	AUC	95 % CI[a]	AUC	95 % CI	AUC	95 % CI
ESR	0.27	0.14–0.41	0.48	0.27–0.70	0.27	0.14–0.41
CRP	0.42	0.28–0.57	0.52	0.25–0.79	0.42	0.26–0.58
PCT	0.61	0.42–0.81	0.92	0.77–1.0	0.56	0.35–0.77
Neopterin	0.58	0.44–0.73	0.90	0.81–0.98	0.52	0.36–0.67
IL-8	0.51	0.34–0.69	0.62	0.36–0.87	0.49	0.31–0.67
IL-10	0.58	0.39–0.78	0.71	0.50–0.92	0.56	0.35–0.76
IL-12	0.40	0.20–0.59	0.34	0.17–0.51	0.42	0.22–0.62
Neopterin / IL-12	0.64	0.46–0.82	0.79	0.62–0.95	0.60	0.41–0.79
IL-10 / IL-12	0.64	0.46–0.82	0.75	0.58–0.93	0.61	0.42–0.80

[a] confidence interval

5.5 Diagnostic accuracy of the studied parameters

Table 6 shows the efficacy of the studied parameters in differentiating infections (n = 56) from neoplastic fever (n = 10) in 66 cancer patients with suspected infection. The cut-off values were based on the Youden index. The highest sensitivity value was obtained for the neopterin to IL-12 ratio (82%) and the next highest for IL-10 (79%), while the highest figures for specificity were demonstrated for IL-8 (90%), the IL-10 to IL-12 ratio (90%) and PCT (80%). The highest positive predictive value was obtained for the IL-10 to IL-12 ratio (96%), IL-8 (94%) and PCT concentration > 0.24 pg/ml (92%). None of the studied

markers had good negative predictive values, while the best, though still very low, values were recorded for the neopterin to IL-12 ratio (33%) and IL-10 (25%). The highest accuracy was demonstrated for the neopterin to IL-12 ratio (77%) and IL-10 (73%).

Table 6. Utility of admission erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), neopterin, interleukin-8 (IL-8), interleukin-10 (IL-10) interleukin-12 (IL-12), neopterin to IL-12 ratio (neopterin/IL-12) and IL-10 to IL-12 ratio (IL-10/IL-12) in 66 cancer patients with suspected infection of whom 56 with infection and 10 patients with neoplastic fever without infection in identifying infections in 66 cancer patients with a suspicion of infection.

Variable	Sensitivity		Specificity		PPV[a]		NPV[b]		Accuracy	
ESR ≥ 100 mm/h[c]	11	(4–23)[d]	80	(44–98)	75	(35–97)	15	(7–28)	22	(13–35)
CRP ≥ 140 mg/l	39	(27–53)	70	(35–93)	88	(69–98)	17	(7–32)	44	(32–57)
PCT ≥ 0.24 pg/ml	59	(45–72)	70	(35–93)	92	(78–98)	23	(10–42)	61	(48–72)
PCT ≥ 0.5 pg/ml	29	(17–42)	80	(44–98)	89	(65–99)	17	(8–30)	36	(25–49)
Neopterin ≥ 11.5 nmol/l	59	(45–72)	60	(26–88)	89	(75–97)	21	(8–40)	59	(46–71)
IL–8 ≥ 70pg/ml	29	(17–42)	90	(56–100)	94	(71–100)	18	(9–32)	38	(26–51)
IL-10 ≥ 1.4 pg/mL	79	(66–88)	40	(12–74)	88	(76–96)	25	(7–52)	73	(60–83)
IL–12 ≥ 20 pg/ml	46	(33–60)	50	(19–81)	84	(66–95)	14	(5–30)	47	(35–60)
Neopterin / IL–12 ≥ 0.15	82	(70–91)	50	(19–81)	90	(79–97)	33	(12–62)	77	(65–87)
IL-10/ IL–12 ≥ 1.44	39	(27–53)	90	(56–100)	96	(78–100)	21	(10–36)	47	(35–60)

[a] PPV = Positive predictive value ,[b] NPV = Negative predictive value, [c] The cut-off values were based on the Youden index , [d] 95% Confidence interval

6 Discussion

6.1 General

Neutropenic infections in cancer patients have been investigated for decades. However, the entity of non-neutropenic infections has not attracted so much interests, although it is an increasingly common and heterogeneous diagnostic problem in cancer patients with a growing number of treatment modalities and their combinations, which immunocompromise the hosts.

Compared to neutropenic infections, which are mainly treated empirically according to the generally accepted guidelines (Pizzo 1999), the management of non-neutropenic infections is not so systematically guided, and the indications for antibiotic treatment are individually determined, mostly based on the origin and focus of the infection. In addition, the severity of these infections is not generally recognized (Freifeld *et al*. 1997).

The severity of infection, the patient's general condition and the state of the immune system as a result of long-lasting, repeated treatments and their combinations often make the decision of how to treat these patients very complicated and overall very heterogeneous. In the course of this clinical study, several attending oncologists made their own decisions, which made the follow-up less rational and the results occasionally insufficient in view of the large number of drop-outs.

The tumor load did not influence significantly the concentrations of the studied parameters within the infection and non-infection groups. Thus, the observed statistically significant differences between the infection and non-infection groups can be assumed to have been caused by infection. After a subdivision of the patients into ones with local and advanced disease, the differences remained statistically significant in all the studied parameters, excluding ESR and IL-8, in the patients with advanced disease. However, the numbers of patients in the study groups were too small to warrant definitive conclusions in this respect, especially concerning the patients with local disease and with neoplastic fever. However, the proportion of patients with neoplastic fever (15%) was in harmony with the literature (Boggs & Frei 1960, Browder *et al*. 1961, Johnson 1996).

It is well known that cancer and its treatments also induce an acute phase response as well cytokine production. When we analysed the influence of cancer treatment on the studied parameters in the infection group (chemotherapy; n = 38 vs. radiotherapy;

n = 15), the only observed difference was the higher median CRP level, probably due to tumour lysis, in the patients with radiotherapy (199 mg/l) compared to the patients receiving chemotherapy (70 mg/l, p = 0.015). These treatment modalities did not cause any statistically significant differences on the concentrations of the other studied parameters or ratios (data not shown). In the non-infection group, 94.4% of the patients were chemotherapy naive and none of them had received radiotherapy. This pilot study did not allow any reliable analyses of different cancers due to the small number of cases. The possible differences should be evaluated in a larger patient population.

ESR and CRP have been used routinely for decades. PCT and IL-8 are newcomers without established diagnostic use. IL-10, IL-12 and neopterin measurements are based on the laborious ELISA method and are therefore mainly used for research purposes. New and easier methods developed, for example, by Immulite® are being introduced clinical practice and enable the use of IL-10, IL-12 and neopterin measurements also in daily routine.

6.2 CRP and ESR

ESR has been routinely used for decades in the diagnosis of infections (Bridgen 1999). In the present study, ESR was not useful in differentiating infections either from non-infections or from neoplastic fever.

High levels of ESR have also been established as evidence of cancer progression in different malignancies, and they also correlate with a poor prognosis (Thynne 1979, Child *et al*. 1980, Thynne & Greening 1980, Margerison & Mann 1985, Sox & Liang 1986, Janssen *et al*. 1987, Imai *et al.* 1990, Henry-Amar *et al*. 1991, Johansson *et al*. 1992, Ljungberg *et al*. 1997, Brigden 1998, Robertson *et al.* 1999a). In our study, the tumor load did not affect the ESR levels.

In earlier studies, the CRP level in cancer patients has been dependent on the tumor load, being higher in patients with metastases than in patients with local disease (Pepys & Baltz 1983). In our series, the tumor load did not have an impact on the CRP level within the study groups. The admission values of CRP were statistically higher in the cancer patients with infection both in local and advanced disease than in the cancer patients without infection. However, CRP was unable to differentiate infections from neoplastic fever. Actually, half of the bacteremic patients in our series had CRP levels < 50mg/L on admission, while the median level of CRP in the neoplastic fever group was as high as 102 mg/L. Thus, CRP is also an unreliable infection marker in cancer patients with suspected infection.

Although CRP turned out to be a poor infection marker on admission, decreasing CRP values differentiated infections from neoplastic fever and the follow-up CRP level in patients with neoplastic fever remained unchanged. This is is in harmony with some earlier studies on febrile neutropenia as well as many other conditions (Santolaya *et al*. 1994, Manian 1995, Rintala *et al*. 1995, Hansson & Lindquist 1997). Follow-up CRP determinations can be used as a method supplementary to the naproxen test in the

differential diagnosis of neoplastic fever (Chang & Gross 1984, Chang & Gross 1985, Economos *et al*. 1995) and they should be investigated prospectively in a larger study population with a sufficient number of patients with neoplastic fever.

6.3 PCT

In cancer patients, the utility of PCT for the diagnosis of infection may be impaired due to the influence of the tumor, as has been reported in patients with medullary C-cell carcinoma of the thyroid and small-cell carcinoma of the lung (Ghillani *et al.* 1989). The underlying cancer was not a major problem for the diagnostic use of PCT in the present series with a false positive rate of 6% (2 out of 36). PCT concentrations were significantly higher in the infection group than in the non-infection group, but after the subdivision, continued to be higher only in advanced disease (Table 2).

PCT has been reported to be a good marker of severe infections (Ghillani *et al.* 1989, Assicot *et al*. 1993, de Werra *et al*. 1997, Gendrel *et al*. 1997, Karzai *et al*. 1997, Monneret *et al.* 1997, Benador *et al.* 1998, Whang *et al.* 1998). This also holds true in the present series of solid tumors for bacteremic patients with an AUC value of 0.92, while its ability to discriminate minor infections from neoplastic fever was less good with an AUC value of 0.58. Thus, PCT turned out to be less sensitive in these non-neutropenic patients with solid tumors than has been earlier reported in association with neutropenic infections in hematologic malignancies (Bernard *et al*. 1998, Lestin *et al.* 1998, Engel *et al*. 1999). In conclusion, PCT did not seem to be sensitive enough in the diagnosis of infections in general in cancer patients.

6.4 Neopterin

Earlier studies have shown that neopterin may be useful in the follow-up of cancer patients in general and particularly, a good marker of cell-mediated immunity (Fuchs *et al.* 1992).

Our results show that the cancer patients with infection had statistically higher neopterin levels than the cancer patients without infection, independently of the stage. Neopterin was a good discriminator for bacteremias (AUC 0.90), but unfortunately not for non-bacteremic (AUC 0.52) infections. Neopterin alone is not sufficient for the diagnosis of infections in cancer patients with infection.

6.5 IL-8

In experimental studies, IL-8 has been shown to be associated with tumor growth (Fujisawa *et al*. 2000, Lee *et al*. 2000**)** and elevated IL-8 levels have been demonstrated in, for example, patients with prostate cancer (Veltri *et al.* 1999). In the present series, the tumor load did not seem to influence the IL-8 concentrations within and between the study groups.

As an infection marker, serial measurement of IL-8 has recently been shown to be a promising tool in predicting bacteremia and preceding chemotherapy-induced fever in neutropenic haematologic patients and neonates (Lindemann *et al.* 1995, de Bont *et al*. 1999, Engel *et al*. 1999, Franz *et al.* 1999b). In addition, IL-8 has also been used as an indicator of the severity of sepsis (Hack *et al*. 1992, Hynninen *et al.* 1997 Hamano *et al.* 1998, Engel *et al*. 1999, Takala *et al.* 1999a).

In the present series, the admission concentration of IL-8 was higher in the patients with infection than in those without infection. However, IL-8 was a poor indicator of bacteremia (AUC 0.62) and useless in differentiating infection from neoplastic fever (AUC 0.51), at least as a single marker and measurement.

6.6 IL-10

IL-10 has a pivotal role in the regulation of responses in cell-mediated immunity, and it favors tumor growth via several pathways (see page 22) (de Waal Malefyt *et al*. 1991, Chen *et al.* 1993, Gimmi *et al.* 1993, Restifo *et al.* 1993, Pretolani *et al.* 1999). Higher serum levels of IL-10 have been recorded in patients with different cancers than in healthy controls, and those levels have also been shown to correlate with the extent of disease (Fortis *et al.* 1996, Avradopoulos *et al*. 1997, Wojciechowska-Lacka *et al.* 1999). In the present study, the tumor load did not have an impact on the IL-10 level within the study groups.

High IL-10 levels have been demonstrated in different types of infection (Watier *et al*. 1993, Marchant *et al*. 1994, van Deuren *et al.* 1994, Vecchiarelli *et al*. 1996). These levels have also been associated with the severity of the subsequent complications (Friedman *et al*. 1997) and even mortality and severe sepsis in febrile patients (van Dissel *et al.* 1998, Gogos *et al*. 2000). In the present study, enhanced IL-10 concentrations were found in cancer patients with but not without infection, and the difference remained significant in the patients with advanced disease after a subdivision of the patients into ones with local and advanced disease. However, IL-10, as a single marker, was inadequate (AUC 0.56) in differentiating infections from neoplastic fever and even less good in identifying bacteremia (AUC 0.71) than PCT (AUC 0.92) and neopterin (AUC 0.90)

6.7 IL-12

In tumor immunology, IL-12 has an opposite role compared to IL-10 as it activates the innate and antigen-specific adaptive immunity against tumor cells and inhibits tumor angiogenesis through INF-γ (Trinchieri 1999). In cancer patients, high IL-12 levels have been shown to be associated with better survival (Lissoni *et al.* 1998). In the present series, the tumor load did not affect the IL-12 contrations within the study groups.

IL-12 is crucial in the early phase of the host defense against microbial infections (Romani *et al*. 1997, Hensler *et al*. 1998a, Trinchieri 1999, van der Poll & van Deventer 1999), and it is produced within a few hours after the onset of infection (Trinchieri 1999). In the present series, the patients in the non-infection group had significantly higher IL-12 levels than the patients in the infection group. After the subdivision of the patients into ones with local and advanced disease, the difference remained significant in those with advanced disease. Because the median duration of the symptoms of infection was at least one day, the possible rise of the IL-12 level induced by infection had already been passed before the serum samples were obtained. The patients in the infection group were probably vulnerable to infections due to their low IL-12 levels. It has been shown earlier after major abdominal surgery that the patients with defective monocyte IL-12 production developed sepsis while those with normal IL-12 production made uneventful postoperative recovery (Hensler *et al.* 1998a). Probably for the above mentioned reasons, IL-12 concentrations were higher in the non-infection patients, and IL-12 was therefore a poor infection marker and not able to differentiate either bacteremic or non-bacteremic infections from neoplastic fever.

6.8 Neopterin and IL-10 to IL-12 ratios

Because the same mediators are often essential in the pathophysiology of both cancer and infection, it is highly unlikely that a single mediator would be able to identify infections in cancer patients. Actually, our results support this hypothesis; none of the studied markers was alone reliable in the differential diagnosis of infections in cancer patients with suspected infections. For this reason, we selected two sensitive infection markers (neopterin and IL-10) and IL-12, which was higher in the patients without infection in this series, and tested whether these combinations would be advantageous in this respect. As far as we know, the neopterin to IL-12 ratio has not been previously evaluated in infection diagnosis.

Both neopterin and IL-12 alone were poor in identifying infection, their sensitivities being 59% vs. 46% and accuracies 59% vs. 47%. However, when we combined these two markers, we obtained a ratio with a relative good sensitivity (82%) as well as accuracy (77%). This ratio was quite a powerful discriminator of bacteremic infections (AUC 0.79). Although the neopterin to IL-12 ratio was less well able to differentiate non-bacteremic infections (AUC 0.60) from neoplastic fever, it was still better than ESR (0.27) or CRP (0.42) in this respect.

The simultaneous determinations of IL-10 and IL-12 are highly feasible, because these cytokines have essential and opposite properties in immunology. Therefore, the balance between these two cytokines has aroused interest in many fields of medicine, such as autoimmune diseases, allograft rejection, arthritis, atherosclerosis, gynecology, ophthalmology, infections and oncology. (Uyemura *et al.* 1996, Yin *et al.* 1997, Huang *et al.* 1998, Muller *et al.* 1998a, Akpek *et al.* 1999, Gao *et al.* 1999, Karussis *et al.* 1999b, Swaminathan *et al.* 1999, Szereday *et al.* 1999, Stolina *et al.* 2000).

In the present series, both the ratio of neopterin to IL-12 (AUC 0.64) and that of IL-10 to IL-12 (0.64) were clearly superior to the classical infection parameters ESR (0.27) and CRP (0.42) in identifying infections in cancer patients in general and even slightly better than PCT (0.61). Actually, these two ratios used simultaneously result in a sensitive (neopterin to IL-12 ratio 82%) and specific (IL-10 to IL-12 ratio 90%) tool for diagnosing infections in cancer patients. This approach should be tested in a larger population of cancer patients with suspected infection.

7 Conclusions

The tumor load was not related to the concentrations of the studied markers within the study groups, and the differences observed between the study groups can hence be assumed to be due to infection. All the markers evaluated, excluding ESR and IL-12, were statistically higher in the infection group than in the non-infection group. After a subdivision of the patients into ones with local and advanced disease, the differences remained statistically significant in the group with advanced disease for all markers except IL-8, and for CRP and neopterin even in local diasease. Although PCT (AUC 0.92) and neopterin (0.90) were good markers for identifying bacteremia, none of the studied parameters alone was powerful enough to differentiate infection in general from neoplastic fever. The ratios of neopterin to IL-12 and IL-10 to IL-12 were best in this respect, both having rather poor AUC values of 0.64.

The diagnosis of infection in adult cancer patients with solid tumors requires combinations of markers, which take simultaneously into account the underlying malignancy and the ongoing infection. The neopterin to IL-12 ratio with its good sensitivity (82%) and the IL-10 to IL-12 ratio with its good specificity (90%) could be applicable in this respect. In the future, such combinations and mediators, including newcomers, such as IL-18, should be investigated prospectively in association with infection and cancer in large populations.

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