Review Article

Neopterin as a biomarker of immune response in cancer patients

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Abstract: With the advent of immunotherapy the topic of biomarkers of immune response is of high interest. Along with the expression of programmed death ligand 1 (PD-L1) or tumor infiltrating lymphocytes (TIL), biomarkers of macrophage activation could be of interest. Neopterin is a biomarker of immune activation increased in different disorders associated with immune activation, including cancer. Neopterin synthesis is induced by interferon-γ that also induces indoleamine 2,3-dioxygenase (IDO), an enzyme catalyzing catabolism of tryptophan to kynurenine. Increased urinary or serum concentrations of neopterin have been associated with poor prognosis across a spectrum of malignant disorders of different primary location. Neopterin concentration in peripheral blood as well as in the tumor microenvironment correlates with phenotypic and functional changes of lymphocytes, indicating immune dysfunction. Increased neopterin concentrations are also accompanied by increased rate of conversion of tryptophan to kynurenine. Increasing neopterin concentrations also accompany side effects of anticancer treatment and could predict subsequent complications. Although almost four decades have elapsed since the discovery of increased neopterin concentrations in cancer patients, the full potential of neopterin as a biomarker in this setting has not been so far realized.

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Introduction

The current management of cancer patients is based on the work of the multidisciplinary team. The involvement of physicians of different specialties has resulted in cure rates that were not imaginable only few decades ago. Among other specialties, laboratory medicine plays an increasingly important role in defining the therapeutic strategy and daily management of cancer patients (1). The importance of laboratory medicine is increasing with the advent of targeted therapy that has transformed the treatment of many tumors. The very concept of targeted therapy implies the presence of a target. In some cases like the human epidermal growth factor receptor (HER)-2 the target is obvious and its expression on tumor cells represents a biomarker guiding the therapy (2). However, in other cases the definition of biomarkers that would predict response to targeted therapies is more difficult and targeted treatments are selected empirically rather than based on biomarkers (3). This is especially true in the case of immunotherapy.

Although the idea of manipulating the immune system

to cure cancer is more than hundred years old, until recently immunotherapy as a method of cancer therapy would be regarded, at best, as experimental (4). This has changed with the advent of monoclonal antibodies targeting immune checkpoints that have shown, first time for an immunological agent, clinically significant and reproducible activity in a substantial proportion of patients across the spectrum of solid tumors (5-8). With the advent of these drugs, the search of predictive and prognostic biomarkers of antitumor immune response is emerging as a topic of fundamental importance. It is time to challenge the prevailing paradigm in cancer biomarker research that has viewed the tumor as a sum of proliferating cancer cells. With the increasing understanding of the role of the host antitumor response, it is hence clear that parameters of the host immune or inflammatory response represent biomarkers that are at least equally important in significance to the properties of tumor cells. Unfortunately, our present knowledge about the prognostic and predictive biomarkers of the host immune response is not only substantially lagging behind the vast body of information we have on biomarkers associated with the tumor cells, but also not keeping pace with the rapid introduction of new active agents, representing a major obstacle in the successful implementation of new immune therapies for cancer.

Immune response and biomarkers in cancer patients in the light of new treatment options

The immune and inflammatory phenomena in response to any insult are mediated not only by the cells of the immune system, e.g., different leukocyte populations, but by virtually any cell and tissue in the body. Cancer cell, unlike bacteria or other invading organisms, is a transformed autologous cell, and, paradoxically, participates also in the host antitumor response. In fact, the involvement of cancer cells in the host response against the tumor represents a mechanism of evasion of immune response.

One of the molecules induced on the tumor cells is programmed death ligand 1 (PD-L1). The interaction between PD-L1 and programmed cell death 1 (PD-1) receptor currently represents the most important target of immune therapies. The PD-1 receptor is expressed on the surface of activated T cells, and its ligands PD-L1 and PD-L2 are expressed on dendritic cells, macrophages or other cells, including transformed malignant cells. Interaction between PD-1 and PD-L1 ensures that the immune system is activated only to a limited extent. This is important to avoid autoimmune reaction. Binding of PD-L1 to PD-1 results in reduction of cytokine production as well as in suppression of T cell proliferation. Overexpression of PD-L1 on tumor cells may lead inhibition of T cells in tumor microenvironment, representing a major mechanism of tumor escape from immune surveillance. Several strategies have been proposed to block cancer resistance to the immune responses and stimulate host antitumor response by blocking immune checkpoints.

Monoclonal antibodies can block binding between PD-1 and PD-L1/PD-L2, representing a mechanism to boost the immune response against cancer cells. In clinical trials blocking of the PD-1 pathway has been resulted in activity in different solid tumors including melanoma, non-small cell lung cancer, renal cell cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma (7-14). Improved clinical outcomes are promising, but not all patients respond to these therapies. Thus, the importance of predictive biomarkers is steadily increasing. Development of biomarkers is crucial for personalized medicine. The selection of patients is critical not only for predicting potential response and benefit, but also for avoidance of serious adverse events in patients who would not respond to immunotherapy treatment. Tumor-associated PD-L1 expression has been proposed as a potential biomarker for PD-1 pathway blockade.

The association of PD-L1 expression and the efficacy of PD-1/PD-L1 checkpoint blockades were investigated in a number of prospective trials. For example, in a study of anti-PD1 antibody nivolumab in previously untreated metastatic melanoma both PD-L1-positive and PD-L1-negative patients treated had improved objective response rate compared to dacarbazine. Among patients with PD-L1-positive tumors the objective response rate was 53% compared to 33% in patients with negative or undetermined PD-L1 status. However, regardless of PD-L1 status, patients in the nivolumab arms had improved overall survival compared to dacarbazine (6). Patients with previously treated clear-cell metastatic renal cell carcinoma had better response to nivolumab according to the PD-L1 status. Median progression free survival was 4.9 months in the PD-L1 ≥5% subgroup versus 2.9 months in the PD-L1 <5% subgroup, respectively. Overall response rate was 31% in the PD-L1 ≥5% subgroup and 18% in the PD-L1 <5% subgroup. However, when a cutoff ≥1% for PD-L1 expression was used to define PD-L1 positivity, the

response rate, median progression-free survival and overall survival were similar in PD-L1–positive and PD-L1–negative patients (12).

Even more marked difference in outcome of anti-PD-1 therapy according PD-L1 expression was observed in patients with non-squamous non-small-cell lung cancer. A clear association between PD-L1 expression and benefit from anti-PD-1 treatment has been demonstrated in this setting (7,9). A clear association between the expression of PD-L1 and benefit from nivolumab or pembrolizumab has been demonstrated in the second-line setting. Moreover, a survival benefit has been demonstrated for pembrolizumab over platinum-based chemotherapy in the first-line setting in patients selected by high PD-L1 expression (14).

However, the utilization of PD-L1 expression as a predictive biomarker has important limitations. Different assays for PD-L1 expression use different cutoff points, different antibodies, and measure expression on different cells constituting the tumor microenvironment. Furthermore, PD-L1 is an inducible molecule, the expression is dynamic according to changes of microenvironment or therapeutic intervention, and evaluation of PD-L1 status at just one time point may not have correct predictive value. Also tumors are heterogeneous, and a discrepancy between primary tumor and metastases for PD-L1 positivity in both directions has already been reported. Finally, the response to PD-1/PD-L1 blockades is independent of PD-L1 expression in some cancers, for example in patients with squamous-cell non-small-cell lung cancer, in whom PD-L1 expression did not impair efficacy (10). Thus, PD-L1 expression is certainly not the only biomarker predicting the efficacy of anti-PD1/PD-L1 therapy. Additional research is needed to identify other biomarkers that play a role in antitumor responses elicited by anti-PD-1/PD-L1 therapies. The best candidates for such biomarkers are parameters currently known to predict outcome in patients with advanced malignancies.

Lymphocytes as predictive and prognostic biomarkers in cancer patients

Long before the emergence of monoclonal antibodies targeting the immune checkpoints it has been recognized that solid tumors are infiltrated by leukocytes. Among the leukocyte populations, lymphocytes are usually the most prominent. Tumor infiltrating lymphocytes (TIL) can be present either in the tumor stroma or directly among the tumor cells. Across a spectrum of different solid tumors it has been demonstrated that the presence of TIL is associated with better prognosis (15,16). In addition, in some tumors, e.g., breast cancer, TIL are predictive of response to therapy (17-19). Preoperative (neoadjuvant) chemotherapy is frequently administered in patients with breast cancer, presenting with a unique opportunity to examine the interaction between the immune system and host response. It has been demonstrated that TIL are among the most significant biomarkers predicting pathological complete response, i.e., complete disappearance of tumor cells after the therapy (18-20).

Although TIL represent powerful prognostic, in some cases, predictive biomarkers of host immune response, a wider utilization of TIL determination in clinical practice has been hampered by the lack of standardization (17). Different monoclonal antibodies defining different lymphocyte populations and different methods have been used across the studies. However, the most significant obstacle to use TIL determination, especially when longitudinal follow up is required, is the need for repeated tumor biopsy. Therefore, the concept of liquid biopsy may also be applied to tumor immunology. Despite an obvious difference between the tumor microenvironment and peripheral blood, peripheral blood lymphocyte counts have also been evaluated as prognostic or predictive biomarkers in cancer patients.

Peripheral blood lymphocytes can be assessed as absolute and relative lymphocyte counts. Another method for the assessment of peripheral blood cell (PBC) lymphocyte count is a ratio to other peripheral blood constituents. Among these count PBC-derived ratios, the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) are most commonly used. PBC and differential count are routinely performed in cancer patients, and it was therefore not difficult to retrospectively analyze the PBC-derived ratios in large cohorts of cancer patients. The PBC-derived ratios have been demonstrated to be increased and to predict mortality or response to therapy across a spectrum of different primary tumors (21-27). As mentioned above these ratios in fact represent relative lymphocyte counts, and the prognostic significance of the parameters further underlines the role of immune system in controlling malignant disorders. However, changes of PBC-derived ratios are non-specific and can be encountered also in non-neoplastic disorders, notably atherosclerosis and its complications (28,29).

The role of monocytes/macrophages and innate immunity in cancer

Although most attention has been focused on lymphocytes as the cell population mediating the adaptive immune response, it has been evident that the innate immunity, specifically monocytes/macrophages, play an important role in the host response to neoplasia (30). Macrophages may play a dual role in cancer control in both being powerful effectors of antitumor response as well as contributing to tumor growth and progression. Tumor-promoting inflammatory response is currently recognized as an essential feature of cancer (31). Macrophages represent an important cell population in the tumor microenvironment, and different subpopulations of monocytes/macrophages can be distinguished in the microenvironment and peripheral blood (15,32).

The macrophages can be studied not only by determining the phenotype of the cells by flow cytometry or immunohistochemistry (15,32). Macrophages are metabolically active and some metabolic pathways are expressed predominantly or almost exclusively in macrophages. Therefore, the activity of macrophages may also be assessed by measuring the products of macrophage metabolism.

With regard to the immune response, metabolic pathways induced by interferon-γ are of particular interest. There are marked differences among mammal species. In rodents, interferon-γ induces inducible nitric oxide synthase (iNOS) resulting in the production of large quantities of nitric oxide that can be assessed by measuring nitrites or nitrates. Nitric oxide has a powerful cytostatic activity against tumor cell lines (33,34). A cofactor for nitric oxide synthesis is 5,6,7,8-tetrahydrobiopterin (35). In human macrophages, interferon-γ induces guanosine triphosphate (GTP) cyclohydrolase that catalyzes the production of 7,8-dihydroneopterin from GTP (36). Although GTP cyclohydrolase is the first enzyme in a metabolic pathway leading to the formation of 5,6,7,8-tetrahydroneopterin, the activities of enzymes distal to this step are negligible in human macrophages, thus resulting in the production of 7,8-dihydroneopterin that is rapidly oxidized to neopterin. The biologic significance of neopterin production by human macrophages is still disputed (37,38). Interestingly, human macrophages produce very little, if any, nitric oxide upon the stimulation.

Another enzyme induced by interferon-γ is indoleamine 2,3-dioxygenase (IDO) that catalyzes the conversion of tryptophan to kynurenine (39,40). The activity of IDO is thought to represent a major mechanism of immune suppression. Physiologically, the activity of IDO is important in pregnancy (41), but IDO could also be one of the principal mechanisms of immune escape in patients with cancer (31,42,43).

While IDO can be expressed by different cell types, including tumor cells, neopterin is thought to be produced almost exclusively by macrophages. In cancer patients neopterin production is mostly the result of chronic macrophage stimulation and reflects the failure of the host to control the tumor. This explains the negative prognostic significance of increased neopterin concentrations.

Neopterin as biomarker of immune activation

Increased neopterin concentrations are encountered in various disorders that are associated with immune activation. High neopterin concentrations have been originally reported in the urine of patients with cancer and viral infections by Wachter *et al.* in 1979 (44). Subsequent studies have demonstrated that neopterin concentrations are increased in different disorders associated with the activation of the immune system (45). Serum neopterin concentrations strongly correlate with urinary neopterin expressed as neopterin/creatinine ratio.

Among infectious diseases neopterin has been extensively studied in patients with human immunodeficiency virus 1 (HIV-1) infection (46-49). Neopterin concentrations are increased early in the infection, correlate negatively with CD4 T cell counts and predict prognosis. High neopterin concentrations have also been reported in patients with viral hepatitis (50,51).

The observation of increased neopterin concentrations in patients with HIV-1 infection, viral hepatitis and other viral infection has led to the use of neopterin to monitor the safety of transfusion. In fact, in Austria neopterin is used in this setting (52).

Increased neopterin concentrations have been reported in patients with atherosclerosis (53,54). Acute myocardial infarction is also accompanied by a marked rise in urinary neopterin concentrations (55). Similarly to cancer or HIV-1 infection, high neopterin concentrations predict mortality for atherosclerosis or its complications (56,57).

As would be expected, high neopterin concentrations have also been reported in patients with different autoimmune disorders (58,59) such as rheumatoid arthritis (58) or systemic lupus erythematosus (60).

Neopterin is also increased in patients with inflammatory bowel disease (59,61,62). Neopterin as a biomarker in autoimmune diseases may be of great interest with the introduction of monoclonal antibodies targeting immune checkpoints. However, so far there is limited information about the biomarkers for monitoring autoimmunity in patients treated with immune checkpoint inhibitors and no information on neopterin is available in this setting.

The utilization of urine as a sample matrix is of advantage, especially when repeated sampling is required. This approach has been successfully employed in patients after organ transplantation. It has been demonstrated that a rise of neopterin concentrations in patients after allograft transplant preceded transplant rejection. Although most data are on patients with kidney transplants, neopterin has also been studied after liver, heart and lung transplantation (63-67). In this setting, neopterin represents an invaluable biomarker for the early diagnosis of transplant rejection.

Neopterin concentrations are also increased during pregnancy (68). Neopterin concentrations are very high in newborns and gradually decrease with age (45). On the other end of the age spectrum, increased neopterin concentrations have been also reported to predict mortality in elderly population (69). This is not surprising considering the fact that neopterin predicts mortality for cancer and atherosclerosis, two principal causes of death.

Prognostic significance of increased neopterin concentrations in patients with cancer

Soon after the original report of increased urinary neopterin concentrations in cancer patients (44), serum or urinary neopterin has been investigated in patients with different primary tumors. Although the proportion of patients with increased neopterin differs according the site of the primary and stage, almost uniformly high neopterin concentrations have been reported to predict poor prognosis.

Serum and urinary neopterin concentrations have been studied extensively in patients with gynecological tumors (70). Several studies have identified neopterin as a prognostic biomarker in gynecological cancer, including cervical carcinoma (71) and ovarian cancer (72). Increased urinary neopterin concentrations have been identified as an independent predictor of poor prognosis in patients with cervical carcinoma, endometrial carcinoma or epithelial ovarian carcinoma. Although urinary neopterin is increased only in limited proportion of patients with breast cancer, increased neopterin is associated with poor prognosis in this most common cancer in women as well (73,74). Increased neopterin concentrations in breast cancer survivors have also been correlated with fatigue (75).

Neopterin has also been studied in patients with gastrointestinal tumors. Urinary neopterin concentrations have been associated with poor prognosis in patients with both early and advanced/metastatic colorectal carcinoma (62,76). Increased neopterin concentrations have also been reported in patients with pancreatic cancer (77) and hepatocellular carcinoma. High urinary neopterin was associated with more pronounced hepatic dysfunction and poor prognosis (78).

Increased neopterin concentrations have also been observed in patients with urological malignancies (79) and, similarly to tumors of other primary locations, especially in more advanced tumors (79). In an early study in patients with prostate cancer, increased neopterin concentrations were associated with higher risk of recurrence and lower survival rates. The treatment was accompanied by decreased neopterin concentrations (80). In patients with renal cell carcinoma, serum neopterin was reported to be elevated compared to controls, with the concentrations increasing with the grade and stage (81).

High neopterin levels have also been reported in patients with hematological malignancies (82-84). Patients with lymphoma high urinary neopterin concentrations correlate with disease activity (85). In patients with multiple myeloma serum neopterin concentrations increase with disease activity and are associated with poor prognosis (86,87).

Increased neopterin concentrations have also been reported to be associated with poor outcome in patients with skin melanoma (88). Serum or urinary neopterin concentrations are increased only in a minority of patients with uveal melanoma. High concentrations have been associated with the presence of metastatic disease (89). High urinary neopterin concentrations are present increased in substantial proportion of patients with carcinomas of the head and neck carcinomas (90). Increased neopterin concentrations have also been reported to predict poor prognosis in patients with squamous cell carcinoma of the head and neck (91). High neopterin concentrations have also been shown to be of prognostic significance in lung cancer (92).

In fact, urinary or serum neopterin concentrations have been examined in tumors of most primary locations. In cancer patients, increased neopterin concentrations have been associated also with other biomarkers of host response. As would be expected, neopterin concentrations

correlate in cancer patients with the concentrations of other inflammatory biomarkers, e.g., positively with C-reactive protein and inversely with albumin (81). An association of urinary neopterin concentrations with urinary zinc and copper excretion has also been reported (93). In different tumor types, a significant inverse correlation has been observed between neopterin and hemoglobin concentrations (94). This indicates that systemic immune activation is associated with alteration of iron metabolism that results in anemia of chronic disease in these patients. Interestingly, no correlation was observed between urinary neopterin and PBC-derived ratios like NLR, LMR or PLR (95).

Systemic neopterin concentrations also correlate with the parameters of the phenotype and function of peripheral blood lymphocytes. In patients with primary and metastatic liver tumors, urinary neopterin concentrations exhibited an inverse correlation with the number of CD4 T cells (96). In fact, in some of the patients the CD4 T cell numbers were decreased to the counts observed in patients with advanced HIV-1 infection. Increased neopterin concentrations were also inversely correlated with the proliferative response of peripheral blood lymphocytes to mitogens (97). These observations indicate that increased neopterin concentrations reflect chronic immune stimulation that is associated with immune system dysfunction.

Neopterin as biomarker in the tumor microenvironment

In cancer patients, neopterin concentrations have been mostly examined in the urine or in the serum. Much less is known about neopterin concentrations in other body fluids. However, the information of biomarkers in these sample matrices may be of interest because some body fluids like ascites, pleural effusion or cerebrospinal fluid in fact represent the tumor microenvironment. In the cases when these samples can be obtained repeatedly, the analysis could provide invaluable insights into the immune response in the microenvironment as opposed to systemic changes.

Malignant ascites frequently accompanies advanced abdominal malignancies. Repeated punctures are required for therapeutic reasons, and samples for the analysis of tumor microenvironment could be obtained during paracentesis. It is obviously impossible to compare ascites fluid neopterin concentrations in cancer patients to normal levels as in healthy individuals the amount of peritoneal fluid is limited and cannot be sampled. On the other hand, neopterin concentrations can be studied longitudinally and an association with other parameters of the immune response can be analyzed.

The information on neopterin concentrations in biological fluids other than serum, urine or ascites in cancer patients is very limited. Neopterin concentrations have been examined in cerebrospinal fluid (98) and saliva of cancer patients (99). It has been demonstrated that salivary neopterin concentrations decrease after the resection of tumor in oral cavity. However, an association of salivary neopterin with periodontal infection complicates the interpretation of neopterin concentrations in saliva (100,101). High cerebrospinal fluid neopterin concentrations have been reported in patients with acute lymphoblastic leukemia or lymphoma involving the central nervous system (98,102).

Utilization of neopterin for monitoring of the effects of anticancer therapy

An increasing armamentarium of anticancer agents exerts its mechanism of action through the activation of the immune system. Moreover, there is evidence that some cytotoxic drugs as well as radiotherapy may induce macrophage activation. A number of studies have reported that administration of cytokines is accompanied by increased neopterin production, which is then reflected by higher urinary or serum concentrations. Increasing neopterin concentrations have been reported after systemic administration of a number of cytokines, including interferon-γ (103), interferon-α (104), granulocyte-monocyte colony stimulating factor (105) or interleukin-12 (106). On the other hand, high pretreatment neopterin concentrations have been associated with less pronounced increase of lymphocyte count and absence of response to interleukin-2 therapy (107,108).

Measurement of neopterin has been used to monitor the effect of immune modulating agents not only systemically, but also in the tumor microenvironment. Rising neopterin concentrations have been reported after intraperitoneal administration of cytokines (109).

Increased neopterin concentrations have been reported not only the administration of agents that activate immune response like cytokines, but also after chemotherapy or radiotherapy (110,111). On the other hand, the data on the effect of monoclonal antibodies targeting immune

checkpoints on serum or urinary neopterin concentrations are virtually absent.

Neopterin and toxicity of anticancer therapy

Side effects represent a principal limitation of anticancer therapy. Paradoxically, with the exception of hematologic toxicity, the use of laboratory methods to predict or even monitor toxicity of anticancer therapy is still relatively limited. In many situations, e.g., mucosal or skin toxicity, the diagnosis and assessment of severity of symptoms still heavily relies on symptoms reported by the patients or on physical examination rather than on exact measurements (112-114).

Gastrointestinal toxicity is, along with hematological toxicity the most frequent side effect of cytotoxic chemotherapy. Surprisingly, the assessment of this common toxicity is still based on the data obtained from the patients like the frequency of bowel movements (114). Different laboratory methods have been proposed for monitoring of gastrointestinal toxicity of anticancer agents. Despite promising results, the measurement of intestinal permeability is difficult to be performed in practice (115,116). Citrulline represents another potential biomarker of intestinal toxicity of chemotherapy or radiation. Interestingly, an inverse correlation was recently observed between serum or urinary neopterin concentrations and citrulline in patients with rectal carcinoma treated with chemoradiation (117). Moreover, neopterin concentrations were increased in patients with complications of therapy and initially increased neopterin concentrations predicted subsequent toxicity. Changes of urinary neopterin concentrations have also been associated with side effects of therapy in patients with head and neck carcinoma treated with chemoradiation (110).

Similarly to situation in patients after organ transplantation, daily monitoring of urinary neopterin concentrations could be of significance in cancer patients. When conserved in a cold and dark environment (e.g., the refrigerator) neopterin is stable for several days and daily monitoring can be performed on an outpatient basis. It has been observed that neopterin concentrations are relatively stable. Neopterin can decrease as a result of tumor control, but a rise of urinary neopterin can herald the presence of serious complications (118).

Neopterin concentrations are also transiently increased after surgery, including cancer surgery. Future studies should examine whether systemic or local (i.e., in wound secretions) neopterin concentrations could serve as biomarkers for monitoring or even predicting complications of cancer surgery, the most important part of multimodality treatment.

Metabolism of tryptophan to kynurenine in patients with cancer correlates with neopterin

As mentioned above, catabolism of tryptophan to kynurenine catalyzed by IDO represents another metabolic pathway induced by interferon-γ. Although tryptophan depletion was first thought to inhibit tumor growth (40) and kynurenine at higher concentrations has direct antitumor activity (119), IDO activity is currently thought to represent a major mechanism of the escape of tumor from the control by the host immune system (42). Kynurenine activates the aryl hydrocarbon receptor, resulting in generation of regulatory T cells (120).

In cancer patients, the concentrations of kynurenine and kynurenine/tryptophan ratios exhibit a significant correlation with neopterin concentrations. However, compared to neopterin, the information on kynurenine and tryptophan concentrations in patients with cancer is more limited. In patients with malignant melanoma, lower serum tryptophan, higher kynurenine/tryptophan ratio and serum neopterin concentrations were associated with significantly inferior survival. A significant correlation was observed between neopterin concentration and kynurenine/tryptophan ratio (88). In patients with lung cancer, the kynurenine/tryptophan ratio was reported to correlate with advanced stage (121). In colorectal cancer patients, serum tryptophan correlated inversely with parameters of quality of life (122). In another study in colorectal cancer, increased kynurenine/tryptophan ratio was observed, and high kynurenine/tryptophan ratio correlated with lymphatic invasion (123). The kynurenine/tryptophan ratio is also increased after cancer surgery (124).

Conclusions

Although almost four decades have elapsed since the discovery of increased neopterin concentrations in cancer patients, the full potential of neopterin as a biomarker has not been so far realized. In cancer patients, increased urinary or serum neopterin concentrations predict poor prognosis. In addition, neopterin measurement could be used to monitor the patients and high neopterin concentrations could predict complications. These data are

gaining importance in an era characterized by the advent of new immunotherapeutic agents.

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Footnote

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