ROLE OF CYTOKINES IN THE DEVELOPMENT OF HEMATOLOGICAL COMPLICATIONS IN ONCOLOGICAL PATIENTS

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Summary. In pathogenesis of hematological complications the essential role belongs to activation of the immune and inflammatory reactions accompanied by increased secretion of cytokines. Data on cytokine contribution in development of hematological complications in oncological patients are summarized in this review.

Key words: cytokines, hematological complications, oncological patients.

Immune mechanisms are important factors in the development of hematological complications in oncological patients. The altered production of cytokines is considered to be essential in immune disorders caused by tumour development and/or carried antitumor treatment. The raised levels of inflammation mediators, cytokines and their receptors, have been registered in cancer patients with localized and metastatic forms of the disease. Activated cytokine production is observed at radio- and chemotherapy. This work presents a dicussion of the role of cytokines in the development of hematological complications in oncological patients.

Anemia

Anemia is a frequent complication in cancer patients. Approximately 40% patients develop anemia by the time of establishment of the diagnosis [1]. In cases of the prescribed radiotherapy the anemia incidence increases and among the patients getting chemotherapeutic medications it may come up to 90% [2]. Anti-inflammatory cytokines such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), along with the other factors play a significant role in anemia pathogenesis. Anti-inflammatory interleukines are responsible for the disordered production of erythropoietin (EPO), depressed proliferation and differentiation of precursor cells, decreased erythrocyte survival rate, disorders in iron metabolism and utilization, and they also determine inadequate response of erythroid

precursors to EPO [3]. Cytokine contribution to the development of anemia in oncological patients has been proved in clinical investigations. The patients with diffuse epithelial ovarian cancer demonstrated negative correlation of IL-6 with hemoglobin (Hb) level [4]. According to Wang et al. [5], increased levels of interferon γ (IF-γ), TNF-α and IL-6 contribute to anemia development in the patients with lymphoma. In the cases of renal cell carcinoma IL-6 is considered to be a significant independent indicator of anemia development [6]. Involvement of cytokines in anemia development in cancer patients was proved with the evidence obtained at blockade of cytokine signaling pathways. The trials included the patients with non-small cell lung cancer revealed that humanized desyalized antibodies to IL-6 ALD518 increased the levels of hemoglobin (Hb), hematocrit, mean corpuscular hemoglobin concentration and raised Hb level more than 12 g/dl in 58% patients with Hb basic level less than 11 g/dl [7]. Experimental model of inflammation anemia in mice proved that antibodies to hepcidin controlled by IL-6 may be effective for the treatment of the patients with anemia of inflammation [8].

Leukocytosis

Leukocytosis observed in cancer patients may relate to release of cytokines, concomitant infection, bone metastasis, undergoing treatment (especially steroids) and other factors [9, 10]. Leukocytosis is quite rarely is a result of hematopoietic cytokines produced by tumour. Cases of leukocytosis due to myelopoiesis inductors produced by tumour were registered in the patients with lung cancer, hepatocellular carcinoma, adenocarcinoma of the pancreas, gallbladder carcinoma, glioblastoma, nasopharingeal carcinoma, esophageal carcinoma, melanoma, gynecological tumours and gastrointestinal cancer [9-14].

The higher frequency of paraneoplastic leukocytosis has been registered in the patients with lung cancer. In the investigation of 227 patients with lung carcinoma the tumour-associated leukocytosis was registered in 33 patients [11]. High serum levels of granulocyte colony-stimulating factor (G-CSF) were revealed in 16 cases, of granulocyte macrophage colony-stimulating factor (GM-CSF) – in 4 cases and of IL-6 – in 18 cases. Examination of 626 patients with metastatic melanoma demonstrated the raised serum levels of G-CSF observed only in 6 patients. Leukocytosis degree in these patients correlated with G-CSF level [12].

It was found out that the tumours producing G-CSF and GM-CSF have more aggressive course and worse prognosis. In cases of thyroid tumour the increased CSF production was registered mainly in the patients with aplastic cancer [13]. Leukocytosis and G-CSF high levels before treatment in these patients are connected as well with unfavourable prognosis. Yamano et al. observed a case of gastric adenocarcinoma which was differentiated well at the early stage but at the advanced stage transformed into the poorly differentiated tumour producing G-CSF [14]. At III and IV stages of lung carcinoma the patients with leukocytosis caused by tumour production of hematopoietic cytokines demonstrated less median survival rate compared to the patients whose tumors didn't produce hemopoietic cytokines.

The measurement of CSF in oncological patients with leukocytosis is obviously rather significant for the prognosis of the disease outcome. The results of experimental works give evidence to consider the usage of antibodies to G-CSF or antisense technologies useful for the treatment of the patients with tumours producing CSF [13].

Lymphopenia

Lymphopenia is often observed in the patients with advanced oncological diseases and serves as a predictor of chemotherapy induced toxicity. CD4+- and CD56+- lymphopenia have the highest prediction value [15]. Number of CD4+-lymphocytes is as well an independent predictor of overall and recurrence-free survival in the patients with metastatic tumours [16].

It is supposed that cytokines may lead to the development of lymphopenia via different mechanisms. The early works in vitro gave evidence of inhibition of early stages of lymphopoiesis by IL-1α, IL-4 and TNF-α [17] and negative regulation influence of IL-3 and IL-1α on early stages of T- and B-lymphopoiesis [18, 19]. Experiments on mice demonstrated that IL-6 stimulation caused uncommitted progenitors to express the Id1 transcription factor, which is known to inhibit lymphopoiesis and elevate myelopoiesis [20]. It has been established that suppressor effect of inflammation mediator neopterin on B-lymphopoiesis is mediated by activation of proinflammatory cytokine genes expression such as TNF-α, IL-6 and TGF-β in stromal cells [21]. There are available evidence of TNF-α involvement in induced apoptosis of T-lymphocyte subpopulations [22, 23]. Suppressor effects of T-regulatory cells, number of which is increased significantly in oncological

patients, are realized by production of cytokines TGF-β, IL-10, IL-35, involved in inhibition of proliferation and activation of immune competent cells [24].

At the same time clinical data about the relation of cytokines and lymphopenia development in oncological patients are limited. In the patients with soft tissue sarcomas lymphopenia was connected significantly with increased serum levels of IL-6, IL-2 soluble receptor and TNF receptor [25]. Our research [26] found out relations between serum levels of IL-10, IL-6, TNF-α and lymphopenia in the patients with uterine cancer treated with radiotherapy.

Recently some clinical investigations have been initiated aimed to reconstitute immune system in oncological patients before and directly after chemotherapeutic treatment to prove the influence of the given therapeutic strategies on overall survival rate. Cytokines IL-2, IL-7, IL-15 and IL-21, belonging to the family which uses common γ-chain of cytokine receptors for transmission of signals are considered to be possible candidates for increasing of number and strtenghthening of fuctional activity of lymphocytes at lymphopenia in oncological patients [27].

Thrombocytosis

Thrombocytosis is a common phenomenon in cancer patients and it serves as a predictor for increased frequency of metastasis and decreased survival rate in these patients [28-30]. Thrombocytosis development in oncological patients may be connected with increased levels of cytokines involved into regulation of thrombocytopoiesis. Thrombocytopoietin as a principal regulator of thrombocyte production as well as other cytokines such as IL-1, IL-4, IL-6, IL-11, TNF play an important role in thrombocytopoiesis [31]. In the research carried out in oncological patients with thrombocytosis the increased levels of thrombopoietic cytokines, mainly thrombopoietin and IL-6, were observed. Patients with solid tumours and reactive thrombocytosis had higher levels of thrombopoietin compared to the patients with no neoplasms with reactive or essential thrombocytosis [32]. In the patients with ovarian epithelial cancer the number of thrombocytes correlated with the levels of IL-6 and thrombopoietin in blood plasma [33]. The correlation of high IL-6 levels in ascytic fluid with the level of circulating platelets was revealed in the patients with this nosology and it allowed to suppose the value of IL-6 for the development of tumour-associated thrombocytosis [34]. The ovarian cancer model in mice allowed to reveal that

increase of thrombopoietin synthesis in liver as a response to IL-6 of tumour origin is a mechanism responsible for the development of paraneoplastic thrombocytosis. It is believed that this mechanism may be involved as well in the development of thrombocytosis in ovarian cancer patients. Use of antibodies to IL-6 reduced significantly the number of platelets in tumor-carrier mice and those affected with ovarian cancer [33]. Normalization of platelet number with the usage of antibodies to IL-6 was observed in the patients with metastatic renal cell carcinoma that suggests IL-6 participation in the development of thrombocytosis in these patients [35]. The revealed thrombocytosis in the patients with refractory cancer who received recombinant IL-6 gives evidence in favour of IL-6 involvement in thrombocytosis development [36].

Thrombocytopenia

Thrombocytopenia is a common symptom in oncological patients. Aplasia of bone marrow due to cytotoxic impact of chemo- or radiotherapy is considered to be a main cause of thrombocytopenia. Bone marrow infiltration with tumour cells, immune thrombocytopenia (ITP) or disseminated intravascular coagulation are more rare causes [37]. The role of cytokines in thrombocytopenia development in oncological patients has not been studied enough. The studies on mice demonstrated that cytokines may be involved in the development of secondary myelodysplastic syndrome caused by antitumor therapy. Cachaço et al. [38] showed that radiation-induced TNF-α causes bone marrow cells apoptosis leading to the decreased levels of leukocytes, megakaryocytes, thrombocytes and development of macrocytic anemia. TNF-α knockout mice demonstrated significantly less apoptosis of the bone marrow cells, sustained number of megakaryocytes and absence of other cytopenias.

Autoimmune thrombocytopenia was observed in the patients with various types of oncological diseases. The most frequently this complication occurs in those patients with the cancer of lungs and breast cancer, less – in the patients with renal cell carcinoma and ovarian cancer [37]. An accelerated destruction of thrombocytes under effect of autoantibodies and disordered production of thrombocytes is seen at ITP. Some evidence is given concerning the role of cytokines in ITP pathogenesis. Some works report about increased proinflammatory cytokines bound with Th1 and Th17 cellular responses in ITP patients [39, 40]. At the same time other authors observed a Th2 cytokine pattern in the

patients with ITP [41]. No researches concerning balance of Th1 and Th2 cytokines in oncological patients with the proved diagnosis of ITP were undertaken.

Minor researches devoted to the study of the origin of thrombocytopenia in oncological patients mention the increased level of certain cytokines suppressing megakaryocytopoiesis and/or stumulating reticuloendothelial system. A case of severe thrombocytopenia in the patient with metastatic colorectal cancer after the 14^{th} cycle of chemotherapy with oxaliplatin was described. Decrease of platelet level was accompanied with the increase of TNF-α and IL-10 levels [42]. Negative correlation was determined between IL-2 and platelet level in our investigation [26]. The obtained data about presence of thrombocytopenia in oncological patients treated with cytokines give evidence in favour of involvement of cytokines in mechanisms connected with thrombocytopenia development. In particular, thrombocytopenia development was observed in oncological patients treated with IL-2 [43] and TNF-α [44]. It was established also that cytokine gene polymorphism may be connected with increased frequency of thrombocytopenia in the patients who received chemotherapy. At treatment with 5-fluorouracil and cysplatin thrombocytopenia was registered more frequently in the patients with IL-6-634 GC and GG genotypes, IL-1β-511 TC and TT genotypes and TNF-α-1031 TT genotype [45].

Eosinophilia

About 5 % of the patients with malignant neoplasms have mild or moderate eosinophilia (within 500/mcl and 1500/mcl). Severe peripheral eosinophilia was registered in the patients with hematological and solid tumours including gastrointestinal cancer, bronchial carcinoma, sarcomas and prostate cancer [46]. It is supposed that eosinophilia in oncological patients may be a result of raised cytokine secretion of immune cells or tumour which are involved in eosinophil proliferation regulation such as IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3 [47, 48].

Development of eosinophilia in oncological patients may be related to the shift in the Th1/Th2 balance to the dominance of Th2 lymphocytes and with increased production of cytokines of Th2-type involved in the development of eosinophilia [49]. Development of eosinophilia in oncological patients was also observed at the treatment with cytokines inducing production of cytokines, promoting development of eosinophilia. Eosinophilia was registered in the patients with platinum-resistant or platinum-refractory ovarian cancer at

treatment with IL-2. Peripheral pull of eosinophils increased significantly after fulfilment of immune therapy and was connected with increase of circulating eotaxin level [50]. Development of eosinophilia was observed in the patients with melanoma at immunotherapy combining peptide vaccine and low systemic dosages of IL-2 [51]. A week after the start of IL-2 subcutaneous injections the circulating levels of IL-5 reached maximum and in 2 weeks significant eosinophilia was registered correlating with IL-5 serum levels. At IL-5 serum peak peripheral blood lymphocyte responses to mitogen indicated temporary shift to Th2 cellular response.

Cases of tumour-associated eosinophilia determined by tumor-derived IL-5 and GM-CSF have been described. Pandit et al. [52] reported of hypereosinophilia and increased IL-5 serum level in the patient with locally disseminated non-small cell lung cancer. Normalizing of the number of eosinophils and IL-5 level after tumourectomy, as well as high tumor cell expression of IL-5 served as evidence of the relation of tumour IL-5 with eosinophilia development. The cases of association between peripheral eosinophilia and the tumour-produced IL-5 were observed as well at hepatocellular carcinoma [53], disseminated gastrointestinal cancer [48], disseminated colon cancer [54]. The correlation of increase in the production of G-CSF and GM-CSF in the tumour tissue with neutrophilia and eosinophilia registered in the patient with thyroid carcinoma [55] and in the patient with large cell carcinoma of lung [56].

Currently, available evidence proves a significant role of cytokines in the development of hematological complications in oncological patients. As the outcome of cancer is determined frequently with complications emerged in different periods in its course, cytokine profile analysis is a topical for oncological patients because of possibility to predict and determine the ways for prevention of complications. Identification of specific cytokines which may serve as biological markers for identification of the patients with high risk of various hematological disorders or their set, determination of levels when cytokines may cause development of symptoms as well as the further elucidation of cytokine-mediated mechanisms involved in the development of hematological complications are important tasks.

References

1. Knight K., Wade S., Balducci L. (2004) Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am. J. Med., 116(7, Suppl. 1): 11–26.

2. Tas F., Eralp Y., Basaran M. et al. (2002) Anaemia in oncology practice: relation to diseases and their therapies. Am. J. Clin. Oncol., 25(4): 371–379.

3. Adamson J.W. (2008) The anemia of inflammation/malignancy: mechanisms and management. Hematology Am. Soc. Hematol. Educ. Program., 2008(1): 159–165.

4. Macciò A., Madeddu C., Massa D. et al. (2005) Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: role of inflammation in cancer-related anemia. Blood, 106(1): 362–367.

5. Wang T., Tu M.F., Zhu J. et al. The role of cytokines in lymphoma with anemia (2013) Zhongguo Shi Yan Xue Ye Xue Za Zhi., 21(2): 392–395.

6. Falkensammer C.E., Thurnher M., Leonhartsberger N., Ramoner R. (2011) C-reactive protein is a strong predictor for anaemia in renal cell carcinoma: role of IL-6 in overall survival. BJU Int., 107(12): 1893–1898.

7. Schuster M. W., Rigas J. R., Orlov S. V. et al. (2010) Inhibition of Interleukin-6 (IL-6) Reverses Anemia In Patients with Advanced Non Small Cell Lung Cancer (NSCLC): Results of a Phase II, Randomized, Double-Blind, Placebo-Controlled Trial Blood. ASH Annual Meeting Abstracts, 116: 640.

8. Sasu B.J., Cooke K.S., Arvedson T.L. (2010) Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia. Blood, 115(17): 3616–3624.

9. Granger J.M., Kontoyiannis D.P. (2009) Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: a retrospective, single-institution study. Cancer, 115(17): 3919–3923.

10. Zalom M., Hussong J., Lopez A. (2012) Carcinoma-produced granulocytemacrophage colony stimulating factor as a cause of severe leukocytosis. Community Oncology, 9(7): 229–231.

11. Kasuga I., Makino S., Kiyokawa H. et al. (2001) Tumor-related leukocytosis is linked with poor prognosis in patients with lung carcinoma. Cancer, 92(9): 2399–2405.

12. Davis J.L, Ripley R.T, Frankel T.L. et al. (2010) Paraneoplastic granulocytosis in metastatic melanoma. Melanoma Res., 20(4): 326–329.

13. Tomisawa Y., Ogasawara S., Kojika M. et al. (2013) Association between Granulocyte Colonies Stimulating Factor (G-CSF) Production and Leukocytosis in Anaplastic Thyroid Carcinoma. Thyroid Disorders Ther., 2(2): 124.

14. Yamano T., Morii E., Ikeda J., Aozasa K. (2007) Granulocyte colonystimulating factor production and rapid progression of gastric cancer after histological change in the tumor. Jpn. J. Clin. Oncol., 37(10): 793–796.

15. Borg C., Ray-Coquard I., Philip I. et al. (2004) CD4 lymphopenia as a risk factor for febrile neutropenia and early death after cytotoxic chemotherapy in adult patients with cancer. Cancer (http://www.ncbi.nlm.nih.gov/pubmed/?term=CD4+lymphopenia+as+a+risk+factor+for+febrile+neutropenia+and+early+death+after+cytotoxic+chemotherapy+in+adult+patients+with+cancer, 101(11): 2675–2680.

16. Péron J., Cropet C., Tredan O. et al. (2013) CD4 lymphopenia to identify end-of-life metastatic cancer patients. Eur J. Cancer., 49(5): 1080–1089.

17. Ryan D.H., Nuccie B.L., Ritterman I. et al. (1994) Cytokine regulation of early human lymphopoiesis. J. Immunol., 152(11): 5250–5258.

18. Hirayama F., Ogawa M. (1995) Negative regulation of early T lymphopoiesis by interleukin-3 and interleukin-1 alpha. Blood, 86(12): 4527–4531.

19. Hirayama F., Clark S.C., Ogawa M. (1994) Negative regulation of early B lymphopoiesis by interleukin 3 and interleukin 1 alpha. Proc. Natl. Acad. Sci. USA, 91(2): 469–473.

20. Maeda K., Malykhin A., Teague-Weber B.N. et al. (2009) Interleukin-6 aborts lymphopoiesis and elevates production of myeloid cells in systemic lupus erythematosus-prone B6.Sle1.Yaa animals. Blood, 113(19): 4534–4540.

21. Minami A., Tsuboi I., Harada T. et al. (2007) Inflammatory biomarker, neopterin, suppresses B lymphopoiesis for possible facilitation of granulocyte responses, which is severely altered in age-related stromal-cell-impaired mice, SCI/SAM. Exp. Biol. Med., 232(1): 134–145.

22. Takano T., Hohdatsu T., Hashida Y. et al. (2007) A "possible" involvement of TNF-alpha in apoptosis induction in peripheral blood lymphocytes of cats with feline infectious peritonitis. Vet. Microbiol., 119(2–4): 121–131.

23. Gupta S., Gollapudi S. (2005) Molecular mechanisms of TNF-alpha-induced apoptosis in aging human T cell subsets. Int. J. Biochem. Cell Biol., 37(5): 1034–1042.

24. Gregori S., Goudy K.S., Roncarolo M.G. (2012) The cellular and molecular mechanisms of immuno-suppression by human type 1 regulatory T cells. Front. Immunol., 3: 30.

25. Ruka W., Rutkowski P., Kaminska J. et al. (2001). Alterations of routine blood tests in adult patients with soft tissue sarcomas: relationships to cytokine serum levels and prognostic significance. Ann Oncol., 12(10): 1423–1432.

26. Сорочан П. П., Прохач Н. Е., Громакова І. А. та ін. (2013) Роль цитокінів у розвитку гематологічних та імунних порушень при променевому лікуванні хворих на рак тіла матки. Укр. радіол. журн. XXI(2): 232–234.

27. Morre M., Beq S. (2012) Interleukin-7 and immune reconstitution in cancer patients: a new paradigm for dramatically increasing overall survival. Target Oncol., 7(1): 55–68.

28. Maráz A., Furák J., Varga Z. et al. (2013). Thrombocytosis has a negative prognostic value in lung cancer. Anticancer Res., 33(4): 1725–1729.

29. Wang H., Gao J., Bai M. et al. (2013). The pretreatment platelet and plasma fibrinogen level correlate with tumor progression and metastasis in patients with pancreatic cancer. Platelets. [В печати].

30. Allensworth S.K., Langstraat C.L., Martin J.R. et al. (2013) Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. Gynecol. Oncol., 130(3): 499–504.

31. Bleeker J.S., Hogan W.J. (2011) Thrombocytosis: diagnostic evaluation, thrombotic risk stratification, and risk-based management strategies. Thrombosis, 2011: 536062.

32. Espanol I., Hernandez A., Cortes M. et al. (1999) Patients with thrombocytosis have normal or slightly elevated thrombopoietin levels. Haematologica, 84(4): 312–316.

33. Stone R.L., Nick A.M., McNeish I.A., et al. (2012) Paraneoplastic thrombocytosis in ovarian cancer. N. Engl. J. Med., 366(7): 610–618.

34. Gastl G., Plante M., Finstad C.L. et al. (1993) High IL-6 levels in ascitic fluid correlate with reactive thrombocytosis in patients with epithelial ovarian cancer. Br. J. Haematol., 83(3): 433–441.

35. Blay J.Y., Rossi J.F., Wijdenes J., et al. (1997) Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma. Int. J. Cancer, 72(3): 424–430.

36. Olencki T., Finke J., Tubbs R. et al. (2000) Phase 1 trial of subcutaneous IL-6 in patients with refractory cancer: clinical and biologic effects. J. Immunother. 23(5): 549–556.

37. Krauth M.T., Puthenparambil J., Lechner K. (2012) Paraneoplastic autoimmune thrombocytopenia in solid tumors. Crit. Rev. Oncol. Hematol., 81(1): 75-81.

38. Cachaço A.S., Carvalho T., Santos A.C. et al. (2010) TNF-alpha regulates the effects of irradiation in the mouse bone marrow microenvironment. PLoS One. 5(2): e8980.

39. Zhang J., Ma D., Zhu X. et al. (2009) Elevated profile of Th17, Th1 and Tc1 cells in patients with immune thrombocytopenic purpura. Haematologica, 94: 1326–1329.

40. Rocha A.M., Souza C., Rocha G.A. et al. (2013) The serum levels of the cytokines involved in the Th17 and Th1 cell commitment are increased in individuals with borderline thrombocytopenia. J. Hematol. Oncol., 6: 28.

41. Jin C.Q., Liu F., Dong H.X. et al. (2012) Type 2 polarized immune response holds a major position in Epstein-Barr virus-related idiopathic thrombocytopenic purpura (EBV-ITP). Int. J. Lab. Hematol., 34(2): 164–171.

42. Koutras A.K., Makatsoris T., Paliogianni F. et al. (2004) Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis. Oncology, 67(2):179–182.

43. Alwan L.M., Grossmann K., Sageser D. et al. (2013) Comparison of acute toxicity and mortality after two different dosing regimens of high-dose interleukin-2 for patients with metastatic melanoma. Target Oncol., [В печати].

44. Meany H.J., Seibel N.L., Sun J. et al. (2008) Phase 2 trial of recombinant tumor necrosis factor-alpha in combination with dactinomycin in children with recurrent Wilms tumor. J. Immunother., 31(7): 679–683.

45. Sakamoto K., Oka M., Yoshino S. Et al. (2006) Relation between cytokine promoter gene polymorphism and toxicity of 5-fluorouracil plus cisplatin chemotherapy. Oncol. Rep. 16(2): 381–387.

46. Todenhцfer T., Wirths S., von Weyhern C.H. et al. (2012) Severe paraneoplastic hypereosinophilia in metastatic renal cell carcinoma. BMC Urol., 12: 7.

47. Anagnostopoulos G.K., Sakorafas G.H., Kostopoulos P. et al. (2005) Disseminated colon cancer with severe peripheral blood eosinophilia and elevated serum levels of interleukine-2, interleukine-3, interleukine-5, and GM-CSF. J. Surg. Oncol., 89(4): 273–275.

48. Fridlender Z.G., Simon H.U., Shalit M. (2003) Metastatic carcinoma presenting with concomitant eosinophilia and thromboembolism. Am. J. Med. Sci. 326(2): 98–101.

49. Lissoni P., Malugani F., Malysheva O. (2002) Neuroimmunotherapy of untreatable metastatic solid tumors with subcutaneous low-dose interleukin-2, melatonin and naltrexone: modulation of interleukin-2-induced antitumor immunity by blocking the opioid system. Neuro Endocrinol Lett., 23(4): 341–344.

50. Vlad A.M., Budiu R.A., Lenzner D.E. et al. (2010). A phase II trial of intraperitoneal interleukin-2 in patients with platinum-resistant or platinum-refractory ovarian cancer. Cancer Immunol. Immunother., 59(2): 293–301.

51. Cragun W.C., Yamshchikov G.V., Bissonette E.A. et al. (2005) Low-dose IL-2 induces cytokine cascade, eosinophilia, and a transient Th2 shift in melanoma patients. Cancer Immunol. Immunother., 54(11): 1095–1105.

52. Pandit R., Scholnik A., Wulfekuhler L., Dimitrov N. (2007) Non-small-cell lung cancer associated with excessive eosinophilia and secretion of interleukin-5 as a paraneoplastic syndrome. Am. J. Hematol. 82(3): 234–237.

53. Balian A., Bonte E., Naveau S. (2001) Intratumoral production of interleukin-5 leading to paraneoplastic peripheral eosinophilia in hepatocellular carcinoma. J. Hepatol., 34(2): 355–356.

54. Kato H., Kohata K., Yamamoto J. et al. (2010) Extreme eosinophilia caused by interleukin-5-producing disseminated colon cancer. Int. J. Hematol., 91(2): 328–330.

55. Nakada T., Sato H., Inoue F. et al. (1996) The production of colony-stimulating factors by thyroid carcinoma is associated with marked neutrophilia and eosinophilia. Intern Med., 35(10): 815–820.

56. Lammel V., Stoeckle C., Padberg B. et al. (2012) Hypereosinophilia driven by GM-CSF in large-cell carcinoma of the lung. Lung Cancer., 76(3): 493–495.