ANTICANCER RESEARCH *34*: 4665-4672 (2014)

Review

The Intercellular Cell Adhesion Molecule-1 (ICAM-1) in Lung Cancer: Implications for Disease Progression and Prognosis

ELIAS A. KOTTEAS, PANAGIOTIS BOULAS, IOANNIS GKIOZOS, SOFIA TSAGKOULI, GEORGE TSOUKALAS and KONSTANTINOS N. SYRIGOS

Oncology Unit GPP, Athens School of Medicine, Sotiria General Hospital, Athens, Greece

Abstract. *The intercellular cell-adhesion molecule-1 (ICAM-1) is a transmembrane molecule and a distinguished member of the Immunoglobulin superfamily of proteins that participates in many important processes, including leukocyte endothelial transmigration, cell signaling, cell-cell interaction, cell polarity and tissue stability. ICAM-1and its soluble part are highly expressed in inflammatory conditions, chronic diseases and a number of malignancies. In the present article we present the implications of ICAM-1 in the progression and prognosis of one of the major global killers of our era: lung cancer.*

Lung cancer, despite all therapeutic efforts, remains the leading cause of cancer-related death worldwide, with approximately 160,340 deaths in the United States in 2012 (1). Its high mortality is largely attributed to early local expansion and metastasis, as most patients present with locally advanced or metastatic (up to 75%) disease at the time of diagnosis (2, 3), while in a large percentage of the remaining patients, early stage disease rapidly progresses to metastatic. Since early-diagnosis provides the only chance for a potentially curative treatment, several studies have focused on the identification of serum biomarkers who could be used as diagnostic, staging, prognostic or predictive markers in lung cancer. Adhesion molecules have been the subject of many of these studies.

Correspondence to: Konstantinos N. Syrigos, MD, Ph.D., Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, 152 Mesogion Avenue, 115 27 Athens, Greece. Tel: +30 2107700220, Fax: +30 2107781035, e-mail: ksyrigos@med.uoa.gr

Key Words: Intercellular cell-adhesion molecule, immunoglobulin, cell signaling, cell-cell interaction, cell polarity, , prognosis, lung cancer, review.

Adhesion between cells and their microenvironment, cell proliferation and cell migration are fundamental for the embryonic development and the establishment and maintenance of cell polarity and tissue architecture (4, 5). These processes are promoted by a variety of cell adhesion molecules in normal tissue. In malignancy, the aberrant expression of cell adhesion molecules results in impaired adhesive properties and cell-cell communication (6, 7). This provides a substratum for neoplastic cells to circumvent the control of differentiation, acquire a malignant phenotype, become motile and invasive and, finally, achieve colonization of distant organs (8, 9). Changes in expression of cell adhesion molecules belonging to the integrin, cadherin and immunoglobulin superfamilies (4) have been observed in several cancer types (10) and associated with tumor progression (6).

The intercellular cell adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin (Ig) superfamily of proteins expressed in several cell types. ICAM-1 plays a key role in inflammatory conditions, nervous system development, immune responses through antigen recognition and lymphocyte circulation and activation (11, 12). Particularly, ICAM-1 is involved in signal transduction across cell membranes, leukocyte-leukocyte, leukocyte-endothelial and leukocyte-epithelial cell interactions, transendothelial migration and adhesion-dependent respiratory bursts (13-15). ICAM-1 shows altered expression in many benign and malignant diseases. The evaluation of the expression of ICAM-1 and its soluble form in lung cancer has gathered significant interest in recent years, although there still remain many questions unanswered. This narrative review focuses on the implications of ICAM-1 in lung cancer evolution and prognosis. A literature review was conducted through the Pubmed and Medline databases, using the lung cancer, intercellular adhesion molecule-1 or ICAM-1, and prognosis as key words. An attempt was made to gather all relevant articles and appropriate references extracted from these

articles to compose this review and, ultimately, evaluate the role of ICAM-1 in lung cancer.

Intercellular Cell Adhesion Molecule-1 (ICAM-1)

Intercellular adhesion molecules (ICAMs) are structurally-related members of the immunoglobulin (Ig) superfamily. Five molecules have already been identified (ICAM-1 to 5) and classified together as they contain two or more of an immunoglobulin-like domain of 90 to 100 amino acids. These immunoglobulin-like domains are expressed on the extracellular portion of the protein (16). ICAM-1 (CD54) is a type I transmembrane protein with a molecular weight of 74-114 kDa, depending on its level of glycosylation. The extracellular portion of ICAM-1 consists of 5 immunoglobulin-like domains. The endoomain has a cytoplasmic tail containing a tyrosine with signaling properties that appears to interact with the cytoskeleton protein, α- actinin, the linker molecule ezrin or cortactin (17). A molecule with a suggested crucial role in ICAM-1 signaling cascades is the hydrolase of guanosine triphosphate (GTPase) Rho member of the Ras family of G-proteins, which interferes with the ligation of ICAM-1 on the plasma membrane during the re-arrangement of the actin cytoskeleton (18). Antibody-crosslinked ICAM-1 molecules lacking cytoplasmic tails were not capable of activating Rho proteins (19). ICAM-1 is expressed constitutively at low levels on vascular endothelial cells and on some lymphocytes and monocytes, macrophages, B- and T- lymphocytes, fibroblasts and epithelial cells (20). Furthermore, ICAM-1 is an accessory molecule stabilizing the T-cell receptor-mediated binding between antigen-presenting cells (APC) and T-lymphocytes. ICAM-1 is a specific ligand for leukocyte-function associated antigen-1 (LFA-1), interleukin-1 (IL-1), tumor necrosis factor-1 (TNF-1) and interferon-γ (IFN-γ) (21). Today, there is enough evidence that ICAM-1 modulates and participates in many key processes such as the maintenance of cell-cell interactions and signal transduction, cytoskeleton rearrangement, leukocyte transmigration during inflammation, T-cell stimulation and neovascularization (7, 12, 22-24). Despite ICAM-1's crucial role in immune responses, it has also been associated with tumor progression and prognosis in various types of cancer, including gastrointestinal cancer, breast cancer and melanoma (25-27). ICAM-1 expression in cancer cells most likely reflects the interaction between the tumor and the immune system. ICAM-1 shows altered expression in many benign and malignant diseases, potentially playing a role in tumorigenesis and enhancing the metastatic ability of malignant tumors (28, 29).

Soluble ICAM-1 (sICAM-1)

Soluble ICAM-1 (sICAM-1) is a molecule with 5 extracellular domains, but no transmembrane and cytoplasmic domains have been detected in the serum. *In vitro* studies have demonstrated that sICAM-1 stimulates proinflammatory cascades (30). Thus, increased levels of sICAM-1 have been found in patients with atherosclerosis and cardiovascular disease, autoimmune disease and in patients with airway inflammation disorders such as asthma and chronic obstructive pulmonary disease (COPD), in many cases reflecting the severity of the disease (31-33). sICAM-1 is the product of the proteolytic cleavage of cell surface ICAM-1, as a part of a negative feedback loop (34). Tumor necrosis factor-1 (TNF-1), interleukin-1 (IL-1) and matrix metalloproteinases (MMPs) act as proteases which are responsible for the shedding of sICAM-1 from the cell surface through phosphathidyl inositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), nuclear factor kappa light-chain-enhancer of activated B cells (NF-KB), extracellular regulated kinase 1/2 (ERK-1/2) and non-receptor tyrosine protein (Src) kinase signaling pathways (35). In malignant disorders, sICAM-1 has the ability to bind to circulating cytotoxic lymphocytes, allowing tumors to escape immune recognition (36). Additionally, sICAM-1 has a substantial role in angiogenesis and stimulates tumor cell growth (37). Increased sICAM-1 levels have been detected in patients with solid and hematological tumors. In most cases, increased sICAM-1 serum concentrations have been correlated with advanced disease stage and dismal prognosis (38-40).

ICAM-1 Expression in Benign and Malignant Bronchial Epithelium

The bronchial epithelium over its large surface area is exposed to physical and infectious agents. As part of the defense system, leukocytes are recruited in order to neutralize any possible threat. However, airway hyper-responsiveness is the result of excessive numbers of interstitial leukocytes, as observed in COPD and asthma (41, 42). The accumulation of leukocytes within the interstitium depends on the recruitment of leukocytes from the blood and interstitial space and the survival of tissue leukocytes. The interaction between LFA-1 and ICAM-1 is a prerequisite for lymphocyte accumulation on lung epithelial cells (43). ICAM-1 is expressed mainly on the surface of activated endothelial cells in the pulmonary vasculature and in type II pneumocytes (44). Migration of leukocytes across the endothelial monolayers is both transcellular and paracellular. On the other hand, the movement of T-cells across the bronchial epithelial barrier requires a 3-step process involving adhesion of T-cells onto the basal surface of the epithelium, recognition of the epithelial junctions by T cells promoted by of LFA-1 on T-cells and ICAM-1 on epithelial cells, and T cell transmigration across the epithelial tight junctions (45). The functional consequences of cytokine-induced up-regulation of ICAM-1 expression by lung cancer cells have been investigated since the early 1990s. The presence of monocytes and T-cell lymphocytes within the

neoplastic cells triggers the release of cytokines which induce the expression of ICAM-1 (46). ICAM-1 has been identified in most cases of all types of non-small cell lung cancer cultured lines (NSCLC) and, rarely, in small-cell lung cancer (SCLC) cell lines. Early experimental *in vitro* studies with squamous cell carcinomas showed that LFA-1-positive tumor-infiltrating lymphocytes actively express messenger ribonucleic acid (mRNA) transcripts for IFN-γ, suggesting that the ability of squamous carcinoma cells to express ICAM-1, usually with basal distribution, is associated with the recruitment and activation of tumor-infiltrating lymphocytes, which, in turn, might up-regulate ICAM-1 expression by tumor cells (46, 47). It was also found that increased surface expression of ICAM-1 on TNF treated NCI H460 and H211 cells is associated with increased adherence to LAK (Lymphokine-activated killer) cells and increased susceptibility to LAK-cell cytotoxicity and that these effects are related, at least partly, to ICAM-1/LFA-1 interaction. The expression of ICAM-1 by tumor cells may be involved in the regulation of their susceptibility to the cytotoxic effect of autologous and allogeneic defensive cells based on the fact that LFA-1 is expressed on mononuclear phagocytes, cytotoxic T-cells, natural killers (NK) and LAK (48).

Other studies, by Passlick *et al*. (49) and Jiang *et al*. (50) have reported that ICAM-1 expression in adenocarcinomas has been found selectively increased in alveolar epithelial cells. Interestingly, all surrounding non-malignant tissue compartments, including lung endothelial cells, pulmonary lymphocytes and interstitial fibroblasts, demonstrated ICAM-1 expression. On the contrary, SCLC lines showed no basal ICAM-1 expression. More recently, the potential role of ICAM-1 in lung cancer progression has been evaluated with the use of monoclonal antibodies against cell surface ICAM-1. Brooks *et al*. (51) examined ICAM-1-positive lung cancer cell lines established in SCID mice. UV3, an antibody against ICAM-1, was administered subcutaneously into the tumor. The antibody managed to slow the growth of all tumors, although it had no curative effect. The researchers observed simolar inhibitory results in cell lines from breast, prostate and pancreatic cancer. In SCLC cell lines (H24, H69, H82), the adherence of cancer cells to cultured vascular endothelium in stasis and flow depends on the expression of ICAM-1. After blocking endothelial ICAM-1, adhesion was reduced. It may be speculated that ICAM-1 is a molecule crucially involved in SCLC endothelial adhesion (52). The decrease in ICAM-1 expression on lung cancer cells may also be the result of TNF suppression through the inhibitory effect of natural killer-B cells (NK-B) to the ICAM-1 promoter. These observations were made after administration of thalidomide in lung cancer patients and immunohistochemical evaluation of tumor specimens (53). The important role of NF-kB in the activation of ICAM-1 was demonstrated in human lung cancer A549 cells. The receptor activator of NF-kB ligand (RANKL), known for its substantial role in osteoclastogenesis and tumor metastasis, directed the migration of A549 cells through interaction with MEK/ERK leading to the activation of NF-kB and resulting in ICAM-1 expression and cell migration (54).

Serum Soluble ICAM-1 in Lung Cancer Patients

In the last 20 years, a growing body of data concerning sICAM-1 serum levels in patients with lung cancer has been collected in an attempt to shed more light on the potential role of sICAM-1 in lung cancer growth, disease progression and prognosis (all available data are summarized in Table I). As already mentioned, in other types of malignancies, elevated serum sICAM-1 levels are associated with extensive tumor burden and poor outcome. Early studies have examined the possible differences in sICAM-1 levels between lung cancer patients, patients with benign lung diseases, healthy smokers and non-smokers (55-61). It has been discovered that the smoking habit *per se is* a main cause of sICAM-1 serum levels increase. Moreover, patients with COPD and asthma showed significantly increased sICAM-1 levels when compared with non-smokers. Patients with lung cancer also demonstrated greatly increased sICAM-1 concentrations when compared to all other studied groups of subjects. Interestingly, no difference in sICAM-1 serum levels and histological ICAM-1 expression between various histological tumor types was observed. The correlation between sICAM-1 levels and ICAM-1 tumor expression has also been evaluated.

Grothey *et al*. analyzed sICAM-1 serum levels in 51 NSCLC patients and 40 healthy individuals (smokers and non-smokers) and performed immunohistochemical analysis of ICAM-1 expression in tumor cells in 20 NSCLC patients. They observed that patients with tumors demonstrating ICAM-1 positivity between 30%-60% had higher sICAM-1 levels compared to those who showed ICAM-1 cell positivity of 0%-1% (55). Disease stage was found to be a factor with significant impact on sICAM-1 baseline levels in the majority of studies. Serum sICAM-1 levels were related to tumor stage in several studies involving NSCLC and SCLC patients, with a remarkable difference between metastatic and localized disease (56, 58-61). However, conflicting results have been published demonstrating no difference between patients with early and advanced disease (58, 62, 64). This controversy can be partially explained by the fact that samples were small and different types of ELISA kits were used.

Recent studies have evaluated the predictive and prognostic role of sICAM-1 during chemotherapy (61, 65). The main issues were, firstly, to investigate whether baseline sICAM-1 levels could be of independent prognostic value despite the responses achieved from chemotherapy; and, secondly,

Table I. *sICAM-1 levels in various studies in lung cancer.*

First author, year, reference number, number of patients (n)	sICAM levels (ng/mL)	Comments
Osaki *et al*., 1996 (39) n=80	Controls: 196.8±54.6 Stage IV lung cancer: 472.8±370.8 (p=0.001)	• sICAM levels showed a significantly positive correlation with tumor size (p=0.0209) • Survival of patients with low sICAM concentrations tended to be longer than in patients with higher concentrations (not significant correlation)
Sprenger *et al*., 1997 (41) n=147	Healthy subjects and patients with benign diseases: 332±102 Lung tumors collectively: 387±176 (p=0.0047)	• No significant differences in sICAM-1 levels between different histological subgroups • Patients with advanced tumor stage had higher sICAM-1 levels (p=0.086) • Patients with liver metastasis had significantly higher sICAM-1 levels compared to other stage IV patients • Patients with cerebral or adrenal metastasis had significantly lower sICAM-1 levels compared to other stage IV patients
Taguchi *et al*., 1997 (43) n=19	Controls: 280±21.3 Lung cancer: 494.2±33.3 (p<0.0001) Stage I-IIIA lung cancer: 410.8±34.7 Stage IIIB-IV lung cancer: 554.9±44.1 (p<0.03)	• No statistically significant differences between different histological groups • No significant difference between non-responders and responders group
Grothey *et al*., 1998 (36) n=51	Healthy smokers: 312.0 Healthy non-smokers: 225.2 Localized NSCLC: 280.6 Metastatic NSCLC: 404 Healthy subjects *vs*. NSCLC patients: (p=0.018) Localized NSCLC *vs*. metastatic NSCLC: (p=0.0013)	• No significant differences in sICAM levels between histological subtypes
Kamiyoshihara *et al*., 2002 (40) n=66	Control group: 117.9±64.1 NSCLC patients: 212.0±106.6 (p=0.002)	• Significant differences between T1 and T2 disease (p=0.042) and between N0 and N2 patients (p=0.042) • No differences in sICAM-1 levels in aging, smoking history, histological type or pathological staging
Sin *et al*., 2004 (45) n=84	Stage I-IIIA NSCLC: 297.7±80.5 Stage IV NSCLC: 333.7±153.9 (p=0.45) LD SCLC: 310.8±149.4 ED SCLC: 385±141	• No significant differences between histological types or between smokers and non-smokers • Overall survival was significantly longer in the low sICAM-1 concentration group of NSCLC patients (p<0.05), but not SCLC patients
Guney *et al*., 2008 (42) n=57	Controls: 1354.73±534.38 NSCLC patients: 1724.07±531.15 (p=0.006)	• No significant differences in sICAM-1 levels in terms of age, histology, number of metastases or response to chemotherapy
Cogali *et al*., 2010 (44) n=62	Controls: 55.8±19 NSCLC patients: 993.85±79.1 SCLC patients: 941.2±111.9 (p<0.001)	• No correlation between sICAM-1 levels and the presence of distant metastasis
Quian *et al*., 2011 (47) n=124	Controls: 183.75±54.9 NSCLC patients: 251.71±72.67 (p<0.001)	• Baseline serum sICAM-1 levels were significantly related to performance status (p=0.011) and disease stage (p=0.001) • Pretreatment serum sICAM-1 levels did not significantly correlate with age, gender or histology

Table I. *continued*

Table I. *continued*.

First author, year, reference number, number of patients (n)	sICAM levels (ng/mL)	Comments
Young *et al*., 2012 (46) n=95	LD SCLC: 305.5 ED SCLC: 388.4 (p=0.008) Stage I-III NSCLC: Stage IV NSCLC: (p=0.31)	• No significant difference in baseline sICAM-1 levels between SCLC and NSCLC patients • After three cycles of chemotherapy, sICAM-1 levels sICAM-1, soluble intercellular cell-adhesion molecule-1; were significantly different between SCLC and NSCLC patients

NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer; LD, limited disease; ED, extensive disease.

whether the decrease in serum sICAM-1 levels after administration of chemotherapy could be used as a surrogate marker of objective response. In 2008, Guney and colleagues (61) measured sICAM-1 serum levels in 57 NSCLC patients before and after combination chemotherapy containing cisplatin and compared them with those of 24 healthy controls. They found that serum sICAM-1 levels decreased after chemotherapy (1724,07 ng/mL before chemotherapy, 1514,17 ng/mL after chemotherapy; p=0.05), independently from chemotherapy response. In the study published by Young *et al*. in 2012 (65), plasma samples from 95 patients with NSCLC (n=48) and SCLC (n=47) chosen from a pool of 1,446 patients who participated in two large multi-center, randomized, phase III trials were analyzed. The first trial enrolled 724 patients with SCLC. They were treated with up to 6 cycles of carboplatin and etoposide chemotherapy every 3 weeks and randomly assigned to receive either oral thalidomide or matching placebo for up to 2 years. The second trial involved a total of 722 patients with stage IIIB or IV NSCLC who were treated with up to four cycles of gemcitabine and carboplatin chemotherapy every 3 weeks and randomly assigned to receive either oral thalidomide or placebo for 2 years. In the biomarker study of 95 patients, serum sICAM-1 was measured before and after 3 cycles of chemotherapy. Sub-group analysis identified a significant relationship between progression-free survival (PFS) and baseline sICAM-1 in SCLC for pooled treatment arms, but not in NSCLC, with a hazard ratio (HR) for progression with high baseline sICAM-1 in SCLC of 2.20 (95% confidence interval, CI. 1.16-4.18; p=0.016). In both NSCLC and SCLC patients, serum sICAM-1 was reduced after chemotherapy. However, reduced sICAM-1 levels could not predict response to chemotherapy (42, 46).

In another study by Quian *et al*. published in 2011 (66), including 124 NSCLC patients who received 4 cycles of platimun-based chemotherapy, the atuhors evaluated serum levels of sICAM-1 at baseline and after every two courses of chemotherapy. Serum sICAM-1 levels were found significantly decreased compared to baseline levels (p=0.012). The median reduction was 21% in responders and 9% in non-responders (p=0.097). For an observed sICAM-1 post-treatment reduction of 11.5%, an objective response to chemotherapy could be predicted with a sensitivity of 62% and specificity of 82% (area under the curve, AUC=0.73. 95% CI=0.59-0.87). Patients with low baseline sICAM-1 levels survived longer than those who had higher baseline concentrations. Survival analysis also demonstrated an independent prognostic role for serum sICAM-1 (HR=1.12, 95% CI=1.01-1.21) (66). In the E4599 phase III study (Bevacizumab approval), 878 patients were randomized to receive paclitaxel and carboplatin with our without bevacizumab. Chemotherapy was repeated every 21 days up to a total of six cycles. Serum from 113/878 patients was collected both before treatment and after two cycles of chemotherapy. Baseline sICAM-1 showed significant associations with response and survival in both groups. Patients with low baseline sICAM-1 levels had a higher response rate (32% *vs*. 4%, p=0.02), better overall survival (p=0.00005) and 1-year survival (65% *vs*. 25%) than those with high sICAM levels, respectively. sICAM-1 levels were also predictive for response. Patients with low sICAM-1 levels (260 ng/ml) demonstrated a response rate of 32%. On the contrary, in the high-sICAM-1 group the response rate was 14% (p=0.02). However, there was no significant decrease in the sICAM-1 levels after 2 cycles of chemotherapy (67).

Serum sICAM-1 levels in malignant pleural effusions have also been an area of interest. In a study of 79 adenocarcinomas of the lung, serum sICAM-1 was confirmed as an independent prognostic factor for PFS (68). sICAM-1 may increase in both inflammatory and malignant effusions. Secretion of sICAM-1 might be a sign of generalized inflammation within the pleural space (69).

Discussion

ICAM-1 expression in lung cancer tissue is particularly prominent in bronchial and alveolar epithelial cells. ICAM-1 expression is not affected by histological type. Tumor tissue ICAM-1 expression and serum sICAM-1 levels are significantly correlated, probably because tumor cells are the source of sICAM-1. This cannot be considered as evidence that the released sICASM-1 contributes to the elevated serum levels found in patients with lung cancer. On the other hand, sICAM-1 levels have been found increased in a number of benign and chronic diseases. Thus, sICAM-1 production could represent a process due to non-specific host defence mechanisms. This case is supported by the observation of elevated sICAM-1 levels in healthy smokers. Membrane-bound ICAM-1 levels stimulate T-cell receptor-mediated cellular immune response. Furthermore, the up-regulation of ICAM-1 expression on tumor cells is followed by the extracellular release of sICAM-1. Shedding of sICAM-1 in the extracellular space may be one of the mechanisms by which tumor cells escape cell-mediated cytotoxicity and lysis by the host cellular immune system. Also, sICAM-1 may prevent T-cell antigen-presenting cells from interacting or modifying the functional status of leukocytes. sICAM-1 may also be produced as a secreted splice variant of ICAM-1 without intracellular domains (70, 71). Circulating sICAM-1 can block lymphocyte attachment to endothelial cells, natural-killer cell toxicity and major histocompability complex restricted T cell-tumor interactions. sICAM-1 increases as part of the immune system process against inflammation or it may act as an immunomodulator.

ICAM-1 seems to play an active role in the metastatic process. We have already mentioned the ability of SCLC cell lines to adhere to vascular endothelium via ICAM-1 expression. Likewise, tumor cells may imitate leukocytes in their adhesion surface and use this pathway for vascular adhesion during haematogenous metastasis (72). Thus, through ICAM-1, two essential conditions of tumor growth are fulfilled – escape from immune surveillance and angiogenesis.

From a clinical point of view, baseline sICAM-1 levels seem to have a prognostic value and may be an independent predictor of the outcome in both NSCLC and SCLC. Also, sICAM-1 levels appear to be closely-dependent on the disease burden. The mechanisms resulting in sICAM-1 responses during disease progression and chemotherapy have not been elucidated. Monitoring sICAM-1 levels during treatment may be an adjunctive marker of response or progression. The increase of sICAM-1 expression during the progression of lung cancer is usually associated with poorer outcome compared to patients with dropping sICAM-1 levels. There might also be a good correlation between objective radiologic response and sICAM-1.The fashion in which serum sICAM-1 levels decrease after the induction of chemotherapy is unclear. However, these conclusions are not definitive. Racial differences among patient cohorts could constitute a source of inconsistency. So, are sICAM-1 levels useful and reliable for making clinical and treatment decisions? Our concluding remark is that sICAM-1 could be a potential surrogate and prognostic marker in lung cancer during first-line chemotherapy. However, taking into account that most of the presented studies enrolled small numbers of patients, the available data needs validation through prospective studies on a much broader scale.

Conflicts of Interest

The Authors report no declarations of interest.

References

1 Siegel R, Naishadham D and Jemal A: Cancer Statistics, 2012. CA Cancer J Clin *62(1)*: 10-29, 2012.

2 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ and Thun MJ: Cancer Statistics, 2005. CA Cancer J Clin *55*: 10-30, 2005.

3 Surveillance EPidemiology and End Results, Cancer Statistics Review. Bethesda: National Cancer Institute; 2010.

4 Springer TA: Adhesion receptors of the immune system. Nature *346*: 425-434, 1990.

5 Tessier-Lavigne M and Goodman CS: The molecular biology of axon guidance. Science *274*: 1123-1133, 1996.

6 Makrilia N, Kollias A, Manolopoulos L and Syrigos K: Cell adhesion molecules: role and clinical significance in cancer. Cancer Invest *27(10)*: 1023-37, 2009.

7 Springer TA: Traffic signals for lymphocyte recirculation and leukocyte emigtration: the multistep paradigm. Cell *76*: 301-314, 1994.

8 Charalabopoulos K, Binolis J and Karkabounas S: Adhesion molecules in carcinogenesis. Exp Oncol *24(4)*: 249-257, 2002.

9 Charalabopoulos K, Papalimneou V and Charalabopoulos A: Adhesion molecules in lung cancer. Exp Oncol *25(1)*: 16-21, 2003.

10 Gogali A, Charalabopoulos K and Constantopoulos S: Integrin receptors in primary lung cancer. Exp Oncol *26(2)*: 106-110, 2004.

11 Zimmerman T and Blanco FJ: Inhibitors targeting the LFA-1/ICAM-1 cell adhesion interaction: design and mechanism of action. Curr Pharm Des *14(22)*: 2128-39, 2008.

12 Lawson C and Wolf S: ICAM-1 signaling in endothelial cells. Pharmacological Reports *61*: 22-32, 2009.

13 Duperray A, Languino LR, Plescia J, McDowall A, Hogg N, Craig AG, Berendt AR and Altieri DC: Molecular identification of a novel fibrinogen binding site on the first domain of ICAM-1 regulating leukocyte-endothelium bridging. J Biol Chem *272*: 435-441, 1997.

14 Sligh JE Jr, Ballantyne CM, Rich DD, Hawkins HK, Smith CW, Bradley A and Beaudet AL: Inflammatory and immune responses are impaired in mice deficient in intercellular adhesion molecule 1. Proc Natl Acad Sci USA *90(18)*: 8529-8533, 1993.

15 Adams DH and Shaw S: Leucocyte-endothelial interactions and regulation of leukocyte migration. Lancet *343*: 831-836, 1994.

16 Smith CW, Marlin SD, Rothlein R, Toman C and Anderson DC: Cooperative interactions of LFA-1 and MAC-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils *in vitro*. J Clin Invest *83*: 2008-2017, 1989.
17 Staunton DE, Dustin ML, Erickson HP and Springer TA: The arrangement of the immunoglobulin-like domains of ICAM-1 and the binding sites for LFA-1 and rhinovirus. Cell *61*: 243-254, 1990.
18 Thompson PW, Randi AM and Ridley AJ: Intercellular adhesion molecule (ICAM)-1, but not ICAM-2, activates RhoA and stimulates c-fos and rhoA transcription in endothelial cells. J Immunol *169*: 1007-1013, 2002.
19 Greenwood J, Amos CL, Walters CE, Couraud PO, Lyck R, Engelhardt B and Adamson P: Intracellular domain of brain endothelial intercellular adhesion molecule-1 is essential for T lymphocyte-mediated signaling and migration. J Immunol *179*: 2099-2108, 2003.
20 Dymicka-Piekarska V and Kemona H: Does colorectal cancer clinical advancement affect adhesion molecules (sp_selectin, sE-selectin and ICAM-1) concentration? Thromb Res *124(1)*: 80-83, 2009.
21 Yang L, Froio RM, Sciuto TE, Dvorak AM, Alon R and Luscinskas FW. ICAM-1 regulates neutrophil adhesion and transcellular migration of TNF-alpha-activated vascular endothelium under flow. Blood *106*: 584-592, 2005.
22 Hubbard AK and Rothlein R: Intercellular adhesion molecule-1 (ICAM-1) expression and cell signalling cascades. Free Radic Biol Med *28*: 1379-1386, 2000.
23 Carpén O, Pallai P, Staunton DE and Springer TA: Association of intercellular adhesion molecule-1 (ICAM-1) with actin-containing cytoskeleton and alpha-actinin. Cell *118*: 1223-1234, 1992.
24 Deng C, Zhang D, Shan S, Wu J, Yang H and Yu Y: Angiogenic effect of intercellular adhesion molecule-1. J Huazhong Univ Sci Technolog Sci *27*: 9-12, 2007.
25 Fujihara T, Yashiro M, Inoue T, Sawada T, Kato Y, Ohira M, Nishiguchi Y, Ishikawa T, Sowa M and Chung KH: Decrease in ICAM-1 expression on gastric cancer cells is correlated with lymph node metastasis. Gastric Cancer *2*: 221-225, 1999.
26 Ogawa Y, Hirakawa K, Nakata B, Fujihara T, Sawada T, Kato Y, Yoshikawa K and Sowa M: Expression of intercellular adhesion molecule-1 in invasive breast cancer reflects reflects low growth potential, negative lymph node involvement and good prognosis. Clin Cancer Res *4*: 31-36, 1998.
27 Johnson JP, Stade BG, Holzmann B, Schwäble W and Riethmüller G: De novo expression of intercellular-adhesion molecule-1 in melanoma correlates with increased risk of metastasis. Proc Natl Acad USA *86*: 641-644, 1989.
28 Huang WC, Chan ST, Yan TL, Tzeng CC and Chen CC: Inhibition of ICAM-1 gene expression, monocyte adhesion and cancer cell invasion by targeting IKK complex: Molecular and functional study of novel alpha-methylene- gamma-butyrolactone derivatives. Carcinogenesis *25*: 1925-1934, 2004.
29 Rosette C, Roth RB, Oeth P, Braun A, Kammerer S, Ekblom J and Denissenko MF: Role of ICAM1 in invasion of human breast cancer cells. Carcinogenesis *26*: 943-950, 2005.
30 Mackay CR, Imhof BA: Cell adhesion in the immune system. Immunol Today *14(3)*: 99-102, 1993.
31 Jiang H, Klein RM, Niederacher D, Du M, Marx R, Horlitz M, Boerrigter G, Lapp H, Scheffold T, Krakau I and Gülker H: C/T polymorphism of the intercellular adhesion molecule-1 gene (exon 6, codon 469). A risk factor for coronary heart disease and myocardial infarction. Int J Cardiol *84*: 171-177, 2002.
32 Kitagawa K, Matsumoto M, Sasaki T, Hashimoto H, Kuwabara K, Ohtsuki T and Hori M: Involvement of ICAM-1 in the progression of atherosclerosis in APOEKnockout mice. Atherosclerosis *160*: 305-310, 2002.
33 Lopez-Campos JL, Calero C, Arellano-Orden E, Marquez-Martín E, Cejudo-Ramos P, Ortega Ruiz F and Montes-Worboys A: Increased levels of soluble ICAM-1 in chronic obstructive pulmonary disease and resistant smokers are related to active smoking. Biomark Med *6*: 805-811, 2012.
34 Champagne B, Tremblay P, Cantin A and St Pierre Y: Proteolytic cleavage of ICAM-1 by human neutrophil elastase. J Immunol *161*: 6398-6405, 1998.
35 Gearing AJ and Newman W: Circulating adhesion molecules in disease. Immunol Today *14*: 506-512, 1993.
36 Tsakadze NL, Sen U, Zhao Z, Sithu SD, English WR and D'Souza SE: Signals mediating cleavage of intercellular adhesion molecule-1. Am J Physiol Cell Physiol *287*: 55-63, 2004.
37 Kevil CG, Orr AW, Langston W, Mickett K, Murphy-Ullrich J, Patel RP, Kucik DF and Bullard DC: Intercellular adhesion molecule-1 (ICAM-1) regulates endothelial cell motility through a nitric oxide- dependent pathway. J Biol Chem *279*: 19230-19238, 2004.
38 Alexiou D, Karayiannakis AJ, Syrigos KN *et al*: Serum levels of E-selectin, ICAM-1 and VCAM-1 in colorectal cancer patients: correlation with clinicipathological features, patient survival and tumour surgery. Eur J Cancer *37*: 2392-2397, 2001.
39 Alexiou D, Karayiannakis AJ, Syrigos KN, Zbar A, Sekara E, Michail P, Rosenberg T and Diamantis T: Clinical significance of serum levels of E-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1 in gastric cancer patients. Am J Gastroenterol *98*: 478-485, 2003.
40 Gruss HJ, Dolken G, Brach MA, Mertelsmann R and Hermann F: Serum levels of circulating ICAM-1 are increased in Hodgkin's disease. Leukemia *7*: 1245-1249, 1991.
41 Barnes PJ: Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol *8*: 183-192, 2008.
42 Medoff B, Thomas S and Luster A: T-cell trafficking in allergic asthma. The ins and outs. Annu Rev Immunol *26*: 205-232, 2008.
43 Dransfield, I, Cabanas, C, Craig, A and Hogg N: Divalent cation regulation of the function of the leukocyte integrin LFA-1. J Cell Biol *116*: 219-226, 1992.
44 Guzman J, Izumi T, Nagai S and Costabel U: ICAM-1 and integrin expression on isolated human alveolar type II pneymocytes. Eur Respir J *7*: 736-739, 1994.
45 Porter J and Hall A: Epithelial ICAM-1 and ICAM-2 regulate the egression of human T cells across the bronchial epithelium. FASEB J *23*: 492-502, 2009.
46 Schardt C, Heymanns J, Schardt C, Rotsch M and Havemann K: Differential expression of the intercellular adhesion molecule (ICAM-1) in lung cancer cell lines of various histological types. Eur J Cancer *29A*: 2250-2255, 1993.
47 Melis M, Spatafora M, Melodia A, Pace E, Gjomarkaj M, Merendino AM and Bonsignore G: ICAM-1 expression by lung cancer cell lines: effects of upregulation by cytokines on the interaction with LAK cells. Eur Respir J *9*: 1831-1838, 1996.

48 Vitolo D, Palmieri MB, Ruco LR, Rendina E, Bonsignore G and Baroni CD: Cytokine production and expression of adhesion molecules and integrins in tumor infiltrating lymphomononuclear cells of non-small cell carcinomas of the lung. Am J Pathol *145*: 1-8, 1994.

49 Passlick B, Izbicki JR, Simmel S, Kubuschok B, Karg O, Habekost M, Thetter O, Schweinberer L and Pantel K: Expression of major histocompatibility class I and class II antigens and intecellular adhesion molecule-1 on operable non-small cell lung carcinomas: frequency and prognostic significance. Eur J Cacner *30A*: 376-381, 1994.

50 Jiang Z, Woda BA, Savas L and Fraire AE: Expression of ICAM-1, VCAM-1, and LFA-1 in adenocarcinoma of the lung with observations on the expression of these adhesion molecules in non-neoplastic lung tissue. Mod Pathol *11*: 1189-1192, 1998.

51 Brooks KJ, Coleman EJ and Vitetta ES: The antitumor activity of an-anti CD54 antibody in SCID mice xenografted with human breast, prostate, non-small cell lung and pancreatic cell lines. Int J Cancer *123*: 2438-2445, 2008.

52 Finzel AH, Reininger AJ, Bode PA and Wurzinger LJ: ICAM-1 supports adhesion of human small-cell lung carcinoma to endothelial cells. Clin Exp Metastasis *21*: 185-189, 2004.

53 Lin YC, Shun CT, Wu MS and Chen CC: A novel anticancer effect of thalidomide: inhibition of intercellular adhesion molecule-1-mediated cell invasion and metastasis through suppression of nuclear factor-kappa B. Clin Cancer Res *12*: 7165-7173, 2006.

54 Chen LM, Kuo CH, Lai TY, Lin YM, Su CC, Hsu HH, Tsai FJ, Tsai CH, Huang CY and Tang CH: RANKL increases migration of human lung cancer cells through intercellular adhesion molecule-1 up-regulation. J Cell Biochem 933-941, 2011.

55 Grothey A, Heistermann P, Philippou S and Voigtmann R: Serum levels of soluble intercellular adhesion molecule-1 (ICAM-1, CD54) in patients with non-small-cell lung cancer: correlation with histological expression of ICAM-1 and tumor stage. Br J Cancer *77*: 801-807, 1998.

56 Lopez-Campos JL, Calero C, Arellano-Orden E, Marquez-Martín E, Cejudo-Ramos P, Ortega Ruiz F and Montes-Worboys A: Increased levels of soluble ICAM-1 in chronic obstructive pulmonary disease and resistant smokers are related to active smoking. Biomark Med *6*: 805-811, 2012.

57 De Vita F, Infusino S, Auriemma A, Orditura M and Catalano G: Circulating levels of soluble intercellular adhesion molecule-1 in non-small cell lung cancer patients. Oncol Rep *5*: 393-396, 1998.

58 Osaki T, Mitsudomi T, Yoshida Y, Oyama T, Ohgami A, Nakanishi K, Nakanishi R, Sugio K and Yasumoto K: Increased levels of serum intercellular adhesion molecule-1 (ICAM-1) in patients with non-small cell lung cancer. Surg Oncol *5*: 107-113, 1996.

59 Kamiyoshihara M, Kawashima O, Otani Y and Morishita Y: Clinical significance of the preoperative serum-soluble intercellular adhesion molecule-1 in non- small cell lung cancer. J Cardiovasc Surg *43*: 729-734, 2002.

60 Sprenger A, Schardt C, Rotsch M, Zehrer M, Wolf M, Havemann K and Heymanns J: Soluble intercellular adhesion molecule-1 in patients with lung cancer and benign lung diseases. J Cancer Res Clin Oncol *123*: 632-638, 1997.

61 Guney N, Soydinc HO, Derin D, Tas F, Camlica H, Duranyildiz D, Yasasever V and Topuz E: Serum levels of intercellular adhesion molecule ICAM-1 and E-selectin in advanced stage non-small cell lung cancer. Med Oncol *2*: 194-200, 2008.

62 Taguchi O, Gabazza EC, Kobayashi T, Yoshida M, Yasui H and Kobayashi H: Circulating intercellular adhesion molecule-1 in patients with lung cancer. Intern Med *36*: 14-18, 1997.

63 Gogali A, Charalabopoulos K, Zampira I, Konstantinidis AK, Tachmazoglou F, Daskalopoulos G, Constantopoulos SH and Dalavanga Y: Soluble adhesion molecules E-cadherin, intercellular adhesion molecule-1, and E-selectin as lung cancer biomarkers. Chest *138*: 1173-1179, 2010.

64 Sin HB, Jung CH, Park HD and Lee SS: The relationship between the intercellular adhesion molecule-1 level and the prognosis of the disease in lung cancer. Korean J Int Med *19*: 48-52, 2004.

65 Young RJ, Tin AW, Brown NJ, Jital M, Lee SM and Woll PJ: Analysis of circulating angiogenic biomarkers from patients in two phase III trials in lung cancer of chemotherapy alone or chemotherapy and thalidomide. Br J Cancer *106*: 1153-1159, 2012.

66 Qian Q, Zhan P, Yu, L, Shi, Y, Cheng J, Wei S, Wang Q and Song Y: Baseline levels and decrease in serum soluble Intercellular cell adhseion molecule-1 during chemotherapy predict objective response and survival in patients who have advanced non-small-cell lung cancer. Clin Lung Cancer *12*: 131-137, 2011.

67 Dowlati A, Gray R and Sandler A: Cell adhesion molecules. Vascular endothelial growth factor and basic fibroblast growth factor in patients with non-small-cell lung cancer treated with chemotherapy with or without bevacizumab – an Eastern Cooperative Oncology Groyp Study. Clin Cancer Res *14*: 1407-1412, 2008.

68 Qian Q, Zhan P, Sun WK, Zhang Y, Song Y and Yu LK: Vascular endothelial growth factor and soluble intercellular adhesion molecule-1 in lung adenocarcinoma with malignant pleural effusion: correlations with patient survival and pleural effusion control. Neoplasma *59*: 433-439, 2012.

69 Hoffmann JC, Krüger H, Lührs J and Hamm H: Detection of soluble adhesion molecules in pleural effusions. Chest *110*: 107-113, 1996.

70 Budnik A,Grewe M,Gyufko K and Krutmann J: Analysis of the production of soluble ICAM-1 molecules by human cells. Exp Hematol *24*: 352-359, 1996.

71 Giavazzi R, Chirivi RG, Garofalo A, Rambaldi A, Hemingway I, Pigott R and Gearing AJ: Soluble intercellular cell adhesion molecule 1 is released by human melanoma cells and is associated with tumor growth in nude mice. Cancer Res *52*: 2628-2630, 1996.

72 Aznavoorian S, Murphy An, Stetler-Stevenson WG and Liotta LA: Molecular aspects of tumor cell invasion and metastasis. Cancer *71*: 1368-1383, 1993.

Received April 24, 2014
Revised June 24, 2014
Accepted June 25, 2014