Cervical cancer incidence, globally, is second only to malignant breast cancer. The main causative factor is thought to be human papillomavirus (HPV) infection as a result of many sexual partners. Despite radiotherapy, chemotherapy and surgical treatment, the survival rate of patients with advanced disease is low. Metastasis is one of the stages of cancerogenesis in which tumour cells acquire the ability to migrate and create tumour secondary foci. Tumour biomarkers, proteins produced by neoplastic cells, quantified in body fluids or in tissues, play a key role in treatment monitoring and in determining the prognosis for further years of life. In recent years, the search for cervical cancer biomarkers has been intensively sought. They can become a decisive factor in making radical treatment and, in the near future, a potential therapeutic goal. The article presents and briefly describes the biomarkers of metastasis in cervical cancer studied in recent years and highlights their potential therapeutic use.

Key words: cervical cancer, metastasis, tumour biomarker, therapy, radio- and chemoresistance.

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Review paper

Biomarkers could facilitate prediction of worse clinical outcome of cancer with special insight to cervical cancer

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Introduction

Cervical cancer is the second most common cancer among women [1]. Human papilloma virus (HPV) infection is considered to be the main causative factor [2]. The HPV vaccine plays a major role in the prevention of cervical cancer [3]. In addition, factors such as smoking, the number of births through the maintenance of the transformation zone on the exocervix for many years in which may facilitate exposure to HPV (although hormonal factors may also be involved) and the use of oral contraceptives are taken into account. Currently, surgery, radiotherapy and chemotherapy are first-line treatments [4]. Despite these methods, the survival rate of patients is different and difficult to predict, and in the advanced stage of the disease extremely poor [3, 4]. Biomarkers have been sought for early diagnosis and prediction of the efficacy of therapy [4].

Metastasis is a process that shows a significant progression of cancer. It is due, among others, to EMT (epithelial-mesenchymal transition), which converts epithelial cells into mobile mesenchymal cells. They cross the barrier of blood and lymph vessels and as CTCs (circulating tumour cells) reach distant parts of the body [5, 6].

Tumour biomarkers are molecules secreted primarily by tumour cells. They are used for screening, diagnosis, prognosis, assessing therapeutic response, and detecting recurrence of cancer disease. In terms of chemistry, they are mostly proteins quantified in body fluids or tissues [7].

The article briefly characterises biomarkers of metastasis in cervical cancer studied in recent years and highlights their potential therapeutic use.

Long non-coding RNAs

The human genome is composed of only 2% of the coding sequences and over 90% is an RNA not coding for proteins. Long non-coding RNAs (lncRNAs) are molecules longer than 200 nucleotides in length. Their abnormal expression mediates in the cancerogenesis and development of malignant tumours. lncRNAs may play an important role in pelvic lymph node metastasis of early-stage cervical cancer [8].

Among many lncRNAs, the particular attention of the researchers has been drawn GAS5 (growth arrest-specific transcript 5), lncRNA-LET (long non-coding RNA-low expression in tumour) and MEG3 (maternally expressed gene 3) molecules.

GAS5 acts as a tumour suppressor. The level of GAS5 in cervical cancer is significantly reduced, which translates into a close association with the development of cancer. It can be an independent marker for predicting the survival of cervical cancer patients and becoming a potential therapeutic target [9].

lncRNA-LET, another example of a suppressor, is in normally involved in the stabilisation of nuclear factor 90 (NF90), which prevents hypoxia-induced invasion and metastasis of tumour cells. Its lower expression, as with GAS5, correlates with significantly shorter cervical cancer survival, making it difficult to design a targeted therapy [10].

MEG3 is lncRNA involved, among others, in the process of apoptosis and cell proliferation. In cervical cancer its level is lowered and correlated with HPV infection, progression of malignancy, and lymph node metastases. This abnormal expression is linked to the DNA methylation process often encountered in the early stage of cancerogenesis and leading to its profound modification. The MEG3 gene has two methylated regions that control its expression. It has been proven that precisely the loss of MEG3 expression is related to the hypermethylation of the promoter region of the MEG3 gene. Significantly, MEG3 levels can be determined not only in diseased tissues but also in plasma, which is a convenient and noninvasive method. The low expression of MEG3 was significantly associated with advanced FIGO stages and lymph nodes metastases. The patients with advanced FIGO stages or lymph nodes metastases tend to have shorter overall survival time. Lowered expression of MEG3 testifies cancer recurrence, but also the poorer prognosis for patients [11].

CCHE1 (cervical carcinoma highly-expressed 1) lncRNA, differs from the above, acting as an oncogenic RNA molecule that promotes invasion of cervical cancer. CCHE1 overexpression is correlated with positive HPV, tumour cell proliferation, tumour progression, tumour size, lymph node metastases, and shorter total survival time of patients with this type of cancer [12].

miRNAs (micro RNAs)

miRNAs are short (21–25 nucleotides), non-coding RNA molecules that control gene expression mainly at post-transcriptional level, through mRNA (messenger RNA) degradation and/or translation inhibition. They thus participate in the process of cell growth, their development, proliferation and death. Depending on the role that they play in relation to individual genes, they can act as both suppressors and oncogenes. Dysregulation within the miRNA has a significant impact on the process of cancerogenesis and tumour progression [3, 4, 13]. MiRNAs derived from neoplastic cells pass into the serum/plasma, providing a highly stable form, making them an almost perfect biomarker in oncology [14].

The number of miRNAs, which are potential biomarkers (and often a therapeutic target) in cervical cancer, is overwhelming. So the article presents the most important of the above.

miRNA-224: High expression of miRNA-224 was reported in cervical cancer, and correlates among others with poorly differentiated cancers, lymph node metastases and high degree of vascularisation. MiRNA-224 was identified as a biomarker helpful in deciding about the use of more radical treatment and predicting the clinical outcome of cervical cancer patients [3].

miR-196a: This particle is one of the miR-196 family members (miR-196a-1, miR-196a-2, miR-196b). Increased levels of miR-196a have been demonstrated in serum and tissue of patients with cervical cancer. MiR-196a contributes to proliferation (inter alia through the interaction of the netrin 4 gene, which plays a significant role in stimulating cell growth), and the migration of tumour cells. Serum miR-196a may be promising biomarker of the start of the metastasis stage [4].

miR-26b: The miR-26b level in cervical cancer is significantly lowered and correlated with tumour development, poor prognosis in human cervical cancer, and higher incidence of lymph node metastasis, which is indicative of its suppressive role in tumour cells. Low miR-26b expression was also observed to be correlated with high recurrence rate in patients, suggesting that miR-26b could serve as a potential biomarker to identify patients at higher risk of relapse [13].

miR-205: As an oncogene modulating the expression of many genes, miR-205 promotes cell proliferation and migration. The high level of serum miR-205 in cervical cancer patients is associated with a low degree of tumour cell differentiation, lymph node metastasis, and thus a shorter overall survival. The concentration of circulating miR-205 might be a potential therapeutic goal, and might improve patients' risk stratification and guide their treatment [14].

miR-34b-5p (elevated level), miR-194-5p (increased level) and miR-494 (lowered level in cervical cancer): These molecules influence expression of genes responsible for the synthesis of Notch1 and Notch2 (transmembrane proteins regulating cell proliferation and differentiation). MiR-34b-5p and miR-194-5p might be used as diagnostic biomarkers and miR-494 as a prognostic predictor for an extremely well-differentiated variant of minimal deviation adenocarcinoma (MDA) in which most of the cells lack the cytological features of malignancy [15].

miR-484: MiR-484 suppresses cellular migration, invasion, and epithelial-mesenchymal transition process of cervical cancer cells through the down-regulation of the transcription suppressor – zinc finger E-box-binding homeobox (ZEB) and the SMAD2 protein expression. MiR-484 plays an important role in tumourigenesis and potential applications as new biomarker with decreased expression in cervical cancer [16].

miR-21: In cervical cancer tissues, miR-21 was found as one of the upregulated miRNAs, which may indicate its role as an oncogene. Probably HPV16 infection affects cellular expression of miR-21. This molecule was identified for the first time as an independent marker for predicting the clinical outcome of cervical cancer patients. MiR-21 could be a good marker for the identification of patients with a higher risk of death, qualified for treatment [17].

Of the remaining miRNAs, promising biomarkers of lymph node metastases in cervical cancer the following should be listed: miR-1246, miR-20a, miR-2392, miR-3147, miR-3162-5p and miR-4484 [18].

Chemokines and atypical chemokine receptors

Chemokines belong to compounds primarily involved in the targeted migration of leukocytes in inflammatory

conditions of the body. They also play a role in the biology of cancer (taking part in, among others, cancer transformation, proliferation, or metastasis) and angiogenesis. Recently examined chemokines along with their receptors are: CXCL12/CXCR4 (C-X-C motif ligand 12/C-X-C motif receptor 4), CXCL13/CXCR5, CXCL16/CXCR6, and CCL21/CCR7 (C-C motif ligand 21/C-C motif receptor 7) [1, 19].

The transcriptional factor NFκB (nuclear factor-κB) is largely responsible for the activation of chemokines. Under normal circumstances, it is associated with its inhibitor. Unfortunately, all molecular changes in tumour cells disturb the regulation of NFκB activity, which contributes, among other things, to activation the discussed cytokines. An example of such a chemokine is SDF-1 (stromal cell-derived factor-1), associated with its CXCR4 receptor, the expression of which increases significantly in cervical carcinoma cells and correlates with the size and malignancy of cancer [20].

Recently, attention of scientists has been attracted to atypical chemokine receptors (ACRs), which are structurally similar to G-protein receptors. However, these receptors do not induce a classic G-protein signal, due to small but significant differences in their structure. The family of atypical receptors for chemokine include: DARC (Duffy antigen receptor for chemokines), D6 (decoy receptor 6), CCX-CKR (chemocentryx chemokine receptor). These receptors have the ability to modify the bioavailability of chemokines. It is believed that they inhibit tumour progression by binding to chemokines and thereby reducing their biological activity. Patients with cervical carcinoma without DARC and CCX-CKR expression are more susceptible to lymph node metastases, and those without D6 receptor are more susceptible to relapse [1].

In recent years, another member of the ACRs – CRAM, more commonly known as CCRL2 (C-C motif receptor-like 2) has been identified. Its expression on cancer cells in cervical carcinoma is, unlike the above-mentioned receptors, increased and associated with lymph node metastasis and shorter overall survival of patients with this cancer [21].

Interleukins

Interleukin 1 (interleukin-1α – IL-1α, interleukin-1β – IL-1β), a key inflammatory cytokine, is secreted by various cell types. In the tumour microenvironment it induces the expression of growth factors such as IL-6, IL-8, TNF-α (tumour necrosis factor α), VEGF (vascular endothelial growth factor), TGF-β (transforming growth factor β), and genes for MMPs (matrix metalloproteinases), and it stimulates the production of proangiogenic proteins.

Interleukin 6, like IL-1, is produced by different cells. In the case of tumour cells it affects their survival, proliferation and migration to the surrounding tissues mainly by activation JAK/STAT3 (Janus kinase/signal transducer and activator of transcription) and Ras/MAPK (Ras/mitogen-activated protein kinase) signalling pathways.

Both interleukins probably play a significant role in cervical cancer, associated with invasion, progression and metastasis. They are also a potential therapeutic target [2].

Hepatoma-derived growth factor

Hepatoma-derived growth factor (HDGF) is a growth factor involved in many processes, such as the development of organs in the foetal life. It is primarily a stimulator of vascular endothelial cell growth. The increase in expression of HDGF, both in the nucleus and in the cytoplasm (as it moves between cytoplasm and the nucleus depending on the cell cycle phase and the degree of cell differentiation) correlates with the cancer genesis. This agent can stimulate angiogenesis and thus tumour progression.

Elevated HDGF level in cervical cancer means poor prognosis for patients (especially after surgery), but it is also a potential goal for therapy for the future [22].

Metastasis-associated in colon cancer 1

Metastasis-associated in colon cancer 1 (MACC1) is a protein that mainly regulates proliferation, migration, and cell colonisation. Mediates the HGF/Met (hepatoma growth factor/met gene) signalling pathway. The surface receptor of the tyrosine kinase, encoded by the *met* gene, is activated by attaching to it the HGF ligand. This process, amplified by other Ras/MAPK or PI3K/Akt (phosphatidylinositol-3-kinase/a threonine kinase) signal pathways, leads to the recruitment of the MACC1 protein. It moves to the cell nucleus and, as a transcription factor, binds to the *met* gene promoter, enabling the synthesis of new receptor molecules for the aforementioned kinase, thereby amplifying the signal.

Incorrect expression of MACC1 (increased in cervical cancer) is associated with a higher degree of tumour, lymph node metastases, and a shorter overall survival. Elevated MACC1 level is a reliable indicator of progression in cervical cancer. The impact on MACC1 protein may in the near future become one of the methods of oncological treatment [23, 24].

Aquaporins

Aquaporins (AQPs) are structures present in many epithelial tissues, regulating fast flow of water driven by an osmotic gradient through the epithelial barrier. Tumour cells, being extremely metabolically active, show increased water requirements.

Increased expression of aquaporin 8 (AQP8), which scientists have highlighted in recent years, is positively correlated with an increase in ERK1/2 (extracellular signal-regulated protein kinase 1 and 2). These mitogen-activated and phosphorylated kinases transfer the signal from the cell surface and affecting transcription factors, regulate cell proliferation, differentiation, and apoptosis. They also play an important role in the process of cancerogenesis.

The AQP8 and ERK1/2 synergism is related to the transition from the preinvascent stage to invasive cervical cancer, including the metastatic stage [25].

Flotillins

Flotillins are mobile, transmembrane proteins of increased expression, among others in the process of cell differentiation. They mediate in many signalling pathways.

Recent studies have shown that elevated flotillin 2 (FLOT2) level correlate with tumour progression and metastasis. In cervical cancer, this means the advancement of the cancer process, and thus the shorter survival time of the patients [26].

Kinesin superfamily proteins

The kinesin protein superfamily (KIF) is a class related to microtubules and ATP (adenosine triphosphate) motor proteins that participate in intracellular transport and cell division. It is divided into 14 families (kinesin 1 – kinesin 14).

KIF14, a representative of the third family of kinesins, plays a significant role in cytokines as well as in proper chromosome alignment and segregation. This particle completes the above functions by interacting with kinases (citron kinase – CIK) and cytokine regulating proteins (protein regulating cytokinesis 1 – PRC1). The absence of KIF14 results in delayed metaphase transition into anaphase, cytokine arrest, and dinuclear cell formation.

Elevated level of KIF14 has been found in many cancers. In cervical cancer, it correlates with a higher degree of tumour progression, chemoresistance and lymph node metastases, and therefore with cancer progression and worse survival rate.

KIF14 can therefore serve as a potential biomarker of chemoresistance and prognostic factor for patients with cervical cancer [27].

Stanniocalcins

Stanniocalcin 2 (STC2) is a glycoprotein present in many tissues. It plays a significant role in regulation of cell metabolism, calcium/phosphorus transport, and homeostasis.

Increased expression of STC2 was observed in many cancers, among others in cervical cancer. It is associated with progression of the disease, lymph node metastases, higher risk of death, and – importantly – cancer cell resistance to radiation therapy. Radioresistance correlates with cell cycle regulation, therefore STC2 "silencing" reduces cell growth by delaying the transition of G0 to G1 phase of the cell cycle. Overexpression of STC2 promotes proliferation (even in spite of hypoxia) and colonisation of tumour cells, thus contributing to resistance to applied therapy.

Stanniocalcin 2 can become a good biomarker in assessing the body's response to radiation therapy (hence, this glycoprotein should be evaluated before initiation of therapy) [28].

β-1,3-N-acetylglucosaminyltransferase-3

Expression of β-1,3-N-acetylglucosaminyltransferase-3 (B3GNT3) is observed in healthy and tumour cells. Under physiological conditions it inhibits FAK (focal adhesion kinase) activity, Akt and ERK, and thus important signalling molecules, inter alia, integrins and growth factors. Cancer cells use it for the L-selectin biosynthesis, which greatly facilitates adhesion to the lymph nodes. It follows that B3GNT3 plays a significant role in the metastasis and migration of tumour cells.

B3GNT3 levels in cervical cancer are elevated and correlates with HPV infection, cancer progression, tumour size, radio- and chemoresistance, pelvic lymph node metastases and recurrence of neoplastic disease.

This enzyme is identified as an independent marker for predicting the clinical outcome of cervical cancer patients [29].

Ki67 (Kiel 67)

It has been found that the Ki67 gene product, a protein that primarily plays a role in cell proliferation, can enhance the activity of cathepsins (lysosomal enzymes – proteases involved in cellular invasion and migration, degrading extracellular matrix components). Tumour-associated macrophages (TAMs) are the primary source of high levels of cathepsin activity in various cancer types. Macrophage-supplied cathepsins markedly enhance the invasiveness of cancer cells. This leads to escape from the body's defence system, and to subsequent further spread.

High Ki67 expression in cervical carcinoma is related to the size of the tumour and the degree of its progression, as well as to lymph node metastases [30].

High-mobility group box 1 protein

High-mobility group box 1 protein is a non-histone, protein-binding protein necessary for gene transcription regulation. The active molecule is secreted by cytokine stimulation, passively, during cell death. It also performs (as an extracellular signalling molecule) many biological functions, being both a cytokine and a growth factor.

HMGB1 levels are elevated in many cancers, including cervical cancer. Necrosis of tumour cells results in the release of HMGB1, enabling invasion and metastasis in two ways. First of all, HMGB1, as a proinflammatory factor, activates the immune system, which destroys also healthy cells, giving cancer cells a chance to migrate. Secondly, HMGB1 tends to bind to RAGE (receptor for advanced glycation end products), a transmembrane protein present on the surface of regulatory lymphocytes (regular T lymphocytes). This leads to the production of IL-10 or conversion of Th1 (T helper cells) to Th2, which results in suppression of the inflammatory response, and thereby avoiding the phagocytosis by certain cancer cells.

HMGB1 may become a potential biomarker of metastasis in cervical cancer [31].

Special AT-rich sequence-binding protein 1

Special AT-rich sequence-binding protein 1 functions as a chromatin organiser that provides binding sites for specialized DNA sequences and participates in regulation of gene transcription and expression. It plays a significant role in the development of thymocytes, Th2 cell activation and epidermal differentiation. The alteration of the chromatin structure by SATB1 results, among others, in expression of 1000 genes, predominantly those that control tumour progression and metastasis, includ-

ing overexpression of genes encoding VEGF, TGF-β, MMPs (2, 3 and 9) and lowered expression of BRMS1 (breast cancer metastasis-supressor 1) and E-cadherin genes. Consequently, SATB1 contributes to cancerogenesis, facilitate tumour invasion and progression.

In cervical cancer positive expression of the discussed biomarker correlates with the degree of tumour progression, lymph node metastasis, relapse, and poor prognosis. SATB1 is also the aim of targeted therapy in the future [32].

Complex GINS

The GINS complex (jap. *go – ichi – ni – san*; consisting of, among others, the GINS2 subunit) plays a key role in the cell cycle (initiation of DNA replication). By interacting with proteins such as CDC45 (cell division control protein 45) and MCM (minichromosome maintenance), it contributes to the correct process of the replication fork creation, as well as being responsible for cell division and chromosome segregation.

Unfortunately, GINS complex also contributes to progression of the cancer. In early-stage cervical cancer, its elevated level is associated with a shorter patient survival period, which means a poor prognosis. It may become a good predictor of the onset of metastasis [33].

Astrocyte elevated gene-1

Astrocyte elevated gene-1 (AEG-1) encodes a protein of the same name and contributes to promote cell proliferation, probably by activating PI3K/Akt or NFκB. It is also responsible for the biodegradation of the BCCIPA (BRCA2 and CDKN1A interacting protein α) gene product – the tumour suppressor.

In cervical cancer, increased AEG-1 expression plays an important role in the progression of the tumour and correlates with tumour size and lymph node metastases [34].

P21-activated kinases

GTPases (Ras, Rho, Rac, CDC42) are a family of G proteins, functioning in the cytosol independently as GTP (guanosine triphosphate) hydrolysis enzymes. P21-activated kinases (PAKs) are serine/threonine kinase proteins (PAK1 – PAK6) which are effectors of Rac and CDC42. These molecules have also been implicated in other cellular processes relevant to tumourigenesis, including angiogenesis, epithelial-mesenchymal transition and metabolism.

Overexpression and/or hyperactivity of PAKs (especially PAK4) have been shown in some tumours. PAKs are an important causative agent of cancerogenesis, acting at the cell cycle stage, promoting angiogenesis and epithelial-mesenchymal transition. They affect the migration of tumour cells and their invasiveness by interacting with proteins such as Met or DGCR6 (DiGorge syndrome critical region gene 6). PAKs increase the resistance to some cytostatics.

The high level of PAK4 correlates with the degree of tumour progression, being a reliable prognostic factor in determining the overall survival of cervical cancer patients [35].

Mixed lineage kinase domain-like protein

Necroptosis (programmed form of necrosis or inflammatory death) plays a significant role in a healthy and sick body. Programmed necrotic cell death is induced, among others, by TNF-α, which in turn activates the RIP (receptor interacting protein) kinases – RIP1 and RIP3, binded to mixed lineage kinase domain-like protein (MLKL). Phosphatidylinositol and cardiolipine are then bound to phosphorylated MLKL, which allows MLKL to escape from the cytosol into the cell membrane. In this way, the disturbance of cell membrane integrity result in necrotic cell death.

It was found that low MLKL expression is associated with poor prognosis for patients with cervical cancer, which may be due to reduced ability of the tumour cells to necrosis. This allows them to survive, further develop and attack the entire body (metastasis).

MLKL can serve as a potential therapeutic target in cervical cancer, mediate in the assessment of the radio- and chemotherapy effect, and constitute a predictive value in forecasting disease status in patients with this cancer [36].

Sphingosine kinase

Sphingosine kinase (SPHK) is a compound belonging to the sphingolipids, performing catalytic (enzymatic) functions. It exist as two isoforms: SPHK1 and SPHK2. SPHK1 catalyzes the phosphorylation of sphingosine, thereby forming S1P (sphingosine-1-phosphate), which plays a crucial role in intra- and extracellular signalling (apoptosis inhibition, cell proliferation, angiogenesis). SPHK2 is an antiproliferative agent.

Elevated expression of SPHK1 is involved in the development and progression of cervical cancer. It is also a novel and independent biomarker for shorter overall survival and relapse-free. Inhibition of SPHK1 with pharmacological inhibitors results in potent antitumour activity in cervical cancer [37].

Transducin β-like protein 1-related protein

Numerous signalling pathways, such as Wnt (*wingless* and *int* genes), JAK/STAT3, are involved in EMT, a key process in metastasis. Recently it turned out that transducin β-like protein 1-related protein (TBLR1), influencing the aforementioned pathways, plays a significant role in the promotion of EMT inter alia by increasing vimentin and fibronectin expression (via transcription factors such as Snail or Twist). The mechanism of this phenomenon is unknown. However, it was proven that elevated TBLR1 level is associated with progression and poor prognosis in cervical cancer [38].

Wnt and β-catenin

The Wnt signalling pathway plays an important role in numerous, key cellular processes. The mediator in this pathway is β-catenin, whose level is regulated by GSK-3β (glycogen synthase kinase-3β). It phosphorylates β-catenin, devoting it to degradation. Activation of Wnt inhibits the action of GSK-3β, which enables the non-phosphory-

lated β-catenin to migrate to the cell nucleus and to react with Tef/Lef transcription factors.

The Wnt pathway is involved in the development of tumour cells, metastasis, and chemo- and radioresistance. The presence of β-catenin in the cell nucleus is a highly reliable indicator of tumour expansion and progression. Pharmacological potential inhibitors of the Wnt/β-catenin pathway may become a panacea in the future for resistance to antineoplastic therapy [39].

Conclusions

Multiple protein or microRNA markers have been recognized to contribute to the progression and recurrence of cervical cancers. Many of them are significantly correlated with FIGO stage, histologic grade, lymph node metastasis, vascular/lymphatic invasion and recurrence. Particular those, which are associated with the chemo- or radioresistance of cervical cancers, have been proposed to be promising and to facilitate the definition for cervical cancer treatment options.

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