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Review

Is there a role for urokinase-type plasminogen activator inhibitors as maintenance therapy in patients with ovarian cancer?

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Abstract

There is abundant evidence that the urokinase-type plasminogen activator (uPA), its inhibitors PAI-1 and PAI-2 (plasminogen activator inhibitor type-1 and type-2) and its cells surface receptor (uPA-R, CD87) play a fundamental role in tumor invasion and metastasis and are of significant prognostic significance for many tumor types. We performed a systematic Med-line search on uPA, PAI, uPA-R and (epithelial) ovarian cancer (EOC). The majority of malignant EOC specimens show moderate to strong immunostating of tumor and stromal cells. Overexpression of u-PA and PAI-1 can be found in more the 75% of primary ovarian carcinomas, in most metastatic EOC samples and all examined epithelial ovarian cancer cell lines. uPA overexpression in primary specimens was significantly associated with tumor stage, grade, residual disease status after cytoreductive surgery, and poor clinical outcome. This may be explained by increased chemoresistance, a lower resectability and more aggressive tumor biology and tumor dissemination in patients with high uPA and PAI-1. Several therapeutical approaches aimed at inhibiting the uPA/uPAR functions have shown to possess anti-tumor effects in vitro and in animal models. When treating a patient with advanced ovarian cancer it may to be assumed that inhibiting the progression of established (micro) metastases may be more therapeutically relevant than trying to destroy all tumor cells which is not possible in most cases with current systemic treatment modalities. Taking into account the role of uPA and PAI in cell detachment, formation of new stroma, tumor cell reimplantation and metastasis uPA inhibition should be further investigated as maintenance treatment in patients with advanced EOC.

Keywords: PAI-1; Urokinase-type plasminogen activator; Maintenance therapy; Ovarian cancer; Plasmin; Psammocarcinoma

Introduction

The urokinase-type plasminogen activator plasmin system represents a family of serine proteases that are involved in many normal physiological processes including clot lysis, wound healing, embryogenesis and tissue remodeling.[1] There is abundant evidence that the urokinase-type plasminogen activator (uPA), its inhibitors PAI-1 and PAI-2 (plasminogen activator inhibitor type-1 and type-2) and its cells surface receptor (uPA-R, CD87), also play a fundamental role in tumor invasion and metastasis.[2,3] Over the last decades many studies have demonstrated that high levels of uPA and PAI-1 are predictive of a poor clinical outcome in several types of cancer including gastric, colorectal, breast, lung and ovarian cancer.[4–17] Individual components of the uPA–uPAR system are reported to be differentially expressed in cancer tissues compared to normal tissues and thus have the potential to be developed as prognostic and/or therapeutic targets.[1] In this paper the literature on the subject is reviewed performing a systematic Med-line search on uPA, uPA-R and PAI in (epithelial) ovarian cancer (EOC). We suggest that the use of UPA

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inhibitors should be further evaluated as maintenance therapy in patients with advanced ovarian cancer.

Function of the u-PA system

The PAI-1 and u-PA axis is one of the most investigated protease systems in cancer.[18] Urokinase Plasminogen Activator is synthetized and secreted by normal and tumor cells. Both the inactive proenzyme form of uPA and proteolytically active uPA bind to a specific glycan lipid-anchored receptor (uPAR, CD87). Urokinase Plasminogen Activator activates the proenzyme plasminogen into broad spectrum serine protease plasmin, which may in turn directly degrade extracellular matrix (ECM) proteins such as fibrin, fibronectin, laminin and proteoglycans or activate certain matrix-degrading enzymes (e.g. procollagenase, matrix metalloproteases).[4] Thus, the uPA-mediated conversion of plasminogen to plasmin creates a powerful proteolytic system capable of remodeling ECM and activating growth factors. Urokinase Plasminogen Activator functions while bound with its high affinity cell membrane receptor uPAR.[1,4] As uPAR lacks a transmembrane domain it is unable to directly initiate downstream signaling without interacting with other molecules (such as epidermal growth factor receptor and specific integrins). Signaling pathways activated following uPA binding to uPAR include MAPK, Jak-Stat and focal adhesion kinase systems.[19] The activation of uPA is controlled by its specific inhibitors PAI-1 and PAI-2.[1,4] Binding of PAI-1 or PAI-2 to uPAR-bound uPA results in the subsequent internalization of the ternary complex, thereby controlling cell surface plasmin generation.[20,21] After endocytosis the complex is degraded, followed by partial recycling of the free form of uPAR to the cell membrane.[21] PAI-1 is not only one of the primary regulators of the fibrinolytic system, but also has dramatic effects on cell adhesion and migration.[22] It has a dual role in cancers as on the one hand it inhibits uPA–uPAR leading to inhibition of invasion and metastasis but on the other hand has been reported to directly facilitate tumor growth and angiogenesis.[1]

The-uPA system and ovarian cancer

The first indications for a role of the uPA-mediated proteolytic system in tumor invasion and metastasis came in 1976 from Astedt and Holmberg who demonstrated high uPA concentrations in cultured ovarian carcinoma tissue.[23] In the following years increased uPA and PAI levels were also found in tumor tissue extracts from patients and in malignant ascites.[20] Expression of uPA and PAI-1 in tissue and serum is significantly higher in patients with epithelial ovarian cancer (EOC) compared to benign ovarian tumor or normal ovarian tissue.[18,24] The majority of malignant EOC specimens showed moderate to strong immunostating of tumor and stromal cells.[24] Overexpression of u-PA and PAI-1 can be found in more the 75% of primary ovarian carcinomas, in most metastatic EOC samples and all examined epithelial ovarian cancer cell lines.[5,6,13–15,18,20,24,25] Urokinase Plasmin Activator overexpression in primary specimens was significantly associated with tumor stage, grade, residual disease status and time to relapse, but not to histologic type in two large series on more than 100 primary epithelial ovarian carcinomas.[15,25] In a smaller analysis Mashiko et al. on the other hand found a high expression of PAI-1 more frequently in ovarian clear cell carcinoma (13/14 positive) compared to that in serous tumors (4/13 positive).[18] Thromboembolic events are more common in patients with EOC compared to most other solid tumors, and it is striking that women with clear cell carcinoma of the ovary even have a 2.5 times greater risk of disease related venous thrombosis then other histologies of EOC, despite adherence to prophylactic guidelines.[26,27] Tissue and serum protein levels of uPA and PAI-1 are associated with short progression free and overall survival time for patients with advanced ovarian cancer, and are an independent prognostic factor in several studies.[5,6,13–15,18,20,24,25] This may be explained by increased chemoresistance, a lower resectability and more aggressive tumor biology and tumor dissemination in patients with high uPA and PAI-1.[14] Coexpression of uPA and CD44 with multiple drug resistance markers (MDR1) was noted in primary and metastatic samples.[25] Alberti et al. could show in vitro that ligand dependent EGFR/NFkB signaling leads to co-expression of IL-6 and PAI-1 in ovarian cancer cell lines and in EOC tissue samples.[13] In silico analysis of four publicly available data sets of EOC gene expression showed a correlation between the expression of IL-6 and PAI-1 in advanced ovarian cancer patients which is associated with resistance to chemotherapy and shorter progression free survival.[13,28]

Pharmacologic inhibition of the uPA-PAI axis

Pharmacologic uPA inhibition inactivates the proangiogenic FGF-2 and VEGF-A pathways which orchestrate angiogenesis.[22] In vitro experiments corroborate that blocking of the uPAr-plasmin system decreases the phosphorylation of the Ras-activated pathway molecules such as FAK, MAPK, KNK, ERK1/2 as well the MEK-activated phosphatidylinositol 3-kinase (PI3K) pathway, and also retarded the dephosphorylation of P-AKT and p-mTOR.[29] These are all important drivers of EOC progression.[28] The antifibrinolytic drug tranexamic acid is a plasmin inhibitor which is used to reduce blood loss in patients with menorrhagia, after trauma or during surgery.[30] In the eighties it has been shown that tranexamic acid has a growth inhibitory effect on human ovarian carcinoma cells grown in vitro and in animal experiments.[31,32] Intraperitoneal injections of tranexamic acid to nude mice treated with cisplatin resulted in a significant inhibition of ascites formation and prolonged survival by 50%.[32] Sigurdsson et al. administered 4–6 g of tranexamic acid a day orally

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