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Letters to the Editor

Autologous cysteine peptidase inhibitors as potential anticancer drugs

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I propose the hypothesis that urinary cysteine peptidase inhibitors (UCPI) may be useful as potential anticancer drugs. Human urine is a convenient and inexpensive source of the autologous proteinase inhibitors to be used to inhibit cysteine endopeptidases *in vivo*.

The pathology of malignant tumors can be characterized by three critical steps: (i) transformation of normal cells into neoplastic ones, (ii) invasion of neoplastic cells into normal tissue and (iii) metastasis of tumor cells to distant organs. My arguments are as follows. There are some hypotheses that cysteine endopeptidases play a fundamental role in carcinogenesis: cathepsin L in neoplastic transformation, and cathepsin B and L in invasion and metastasis. Cathepsin L (the isoenzyme presented in normal tissues) is the major protein synthesized in transformed cells by the *ras* oncogene and this enzyme may play a role in malignant transformation by selectively hydrolyzing growth factor receptors.[1] In cell cultures light kininogene, and some other specific inhibitors of cysteine peptidases, inhibit neoplastic transformation. Tumor cathepsins B and L, secreted from cancer cells, play a role in the destruction of host tissue during the neoplastic enzymatic cascade. The localization of cathepsin B at the tumor–host border suggests an important role for this enzyme in tumor invasion.[2] Tumor cathepsin B-like enzyme also plays a role in metastasis via its proagregatory activity and possible procoagulant activity. It can be inhibited by selective cysteine peptidase inhibitors such as light kininogene, mammalian cystatins and specific synthetic inhibitors.[3] Tumor cathepsin B is able to degrade laminin, a basement membrane adhesive glycoprotein that has been shown to facilitate the attachment of metastatic tumor cells to other matrices.[4] The physiological role of multiple forms of human melanoma cysteine peptidase inhibitors in carcinogenesis may be related to their enhancement of the defense mechanism of the host against tumor growth.[5] The cysteine peptidase inhibitors appear in urine from tissues and blood. Autologous urinary cysteine peptidase inhibitors *in vivo* can potentially: (i) stop neoplastic transformation, (ii) inhibit tumor cathepsin B activity at the tumor–host border, (iii) prevent tumor cell induced platelet aggregation and (iv) inhibit hydrolysis of laminin. In the proposed project, the patient's own urine can be used as a convenient and inexpensive source of inhibitors existing in the human body. Urine is the main source for the isolation of large amounts of 'own' non-toxic and non-antigenic (because of self) cysteine peptidase inhibitors. UCPI can be isolated from human urine by affinity chromatography on Sepharose 4B–papain. About 90% of these inhibitors (free and recovered from complex forms) can be isolated by this method.[6] The obtained UCPI, dialyzed and filtered on bacterial syringe filters, could be used as a potential anticancer drug. My own results (unpublished) demonstrate that serum cysteine endopeptidases of patients with malignant tumors can be inhibited *in vivo* with UCPI and that this preparation is not toxic and not antigenic for patients. We are continuing this experimental therapy at the Hospital of Oncology in Wrocław. Our data indicate a protective effect of UCPI against serum cysteine endopeptidases *in vivo* and that UCPI can have a potential effect in tumor therapy via specific inhibitors complexed with the serum tumor cysteine endopeptidases. I would also propose simultaneous measurement of cathepsins (B and L) and procathepsin B as a marker of potential tumor aggressivity. Furthermore, assays of the activators of cysteine peptidases (cathepsin B and papain), and of CPI[37] active cysteine peptidase inhibitors and

CPI^{60} total activity of cysteine pep-tidase inhibitors can be used as markers of the total defense of 'own' organism. I would also propose determination of the difference between CPI^{60} and CPI^{36} (ΔCPI) to find out the amount of the complex of inhibitors with cysteine endopeptidases. The parameters, taken as a ratio of the levels of 'tumor aggressivity' and 'defense of organism', might be useful in the diagnosis of a cancer, as well as in new efficient therapy.[7,8]

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Intrapleural and intraperitoneal palliative treatment of malignant effusions with mitoxantrone

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In a recent article, Torsten *et al.*[1] investigated the effect of intrapleural mitoxantrone. They found that malignant pleural effusion could be stopped for a mean period of 3.2 months in 11 of 12 patients.

Mitoxantrone has several characteristics that make it an optimal drug for local administration, i.e. high local advantage of its pharmacokinetics, extensive tissue binding, steep dose-dependent cytotoxicity and good tolerability by the tissue.[2,3] Since 1991 we treated seven patients with malignant effusions (three pleural and four peritoneal) with intracavitary administration of mitoxantrone. All patients were refractory to systemic chemotherapy. Pleural or peritoneal effusions were drained as completely as possible by simple needle aspiration. Mitoxantrone, dissolved in 100 ml of physiologic saline (20 mg for pleural effusion, 40 mg for peritoneal effusion), was instilled into the cavity via a catheter. Response was defined as follows. Complete response (CR) meant that there was no reaccumulation of fluid or no progression of the residual small effusion within the first 30 days. Partial response (PR) was defined as the relapse of effusion up to 50% of the pretreatment condition. Progressive disease (P) was accepted as the relapse of the effusion of more than 50% of the initial fluid. While four of the patients with malignant peritoneal effusion had PR, three patients with pleural effusion showed progression after 2 weeks of mitoxantrone instillation. The durations of responses with peritoneal effusion were 7, 8, 9 and 16 weeks. All patients with pleural effusion died within 2 months. Two patients with peritoneal effusion died within 4 months and two were alive at 4 months with relapse of the effusion (Table 1).

The results of our study do not support the idea[1,4] that local therapy with mitoxantrone is useful in the

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