Pentoxifylline- rescue for the oncological patient.

Anticancer and protective properties of an alkaloid derivative.

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Abstract

Context: Pentoxifylline is a methylxanthine derivative. Because of influence on blood flow it is a drug used in circulatory diseases. Currently pentoxifylline is under examination as regards its anticancer properties.

Objective: The authors gathered and systemized the knowledge about anticancer activity of pentoxifylline and knowledge about the progress of studies and clinical trials in this subject.

Methods: More than 80 English-language abstracts were analyzed and complete texts of selected articles were obtained from PubMed and the National Cancer Institute at the National Health Institute in USA databases were searched. Data were collected in February 2012.

Results: Compiled data revealed that pentoxifylline prevents cachexia and metastasis, also strongly affects mechanisms of apoptosis in many cell lines by various ways of action. Additionally drug augments the process of apoptosis in combination with other anticancer drugs such as cisplatin, doxorubicine, suramin. The compound plays a role in multidrug resistance by downregulation of P-gp expression. Pentoxifylline is now in the phase of clinical trials in the National Cancer Institute at the National Health Institute in USA in patients with various kinds of cancer.

Conclusion: Pentoxifylline is very promising drug as regards its anticancer and supportive activity in chemo- and radiotherapy, especially as regards preventing veno-occlusive disease. Also important and promising is the augmenting role of pentoxifylline in the process of apoptosis in combination with anticancer drugs used in antitumor regimen.
Introduction

More than 60% of the current anticancer drugs originate from natural sources. New derivatives of those compounds have been produced for many years. Many of these derivatives are in clinical use and new ones are still being searched for. By modifying the already known derivatives of plant metabolites, drugs with increased potency, increased selectivity or a completely new level of action are synthesized. Examples of such metabolites are xanthines, from which methylxanthines are synthesized. Xanthines and their derivatives have become the focus of interest nowadays. This group of alkaloids possesses a wide range of biological activities and some of them have been used in the treatment of many diseases. Relatively recently some of these alkaloids have been examined as regards their antineoplastic properties. One of them- pentoxifylline seems to be very promising in the treatment of cancer since it possesses proapoptotic properties. Cancer is an aggressive disease, known to exist as long as humanity has existed and is currently the main cause of deaths worldwide. One of the most frequently diagnosed cancers globally is breast cancer with over a million cases annually. The multistep event of metastatic cancer involves the invasion of carcinoma cells into the flanking tissues, paving their way to enter the systemic circulation, intravasating to target sites: the bones, lungs and central nervous system. There has been a huge progress in the recent years in the development of therapeutic strategies, but the survival rates for patients with metastatic disease have not changed a lot. The main problem with the used drugs is their high degree of cytotoxicity and the induction of resistance culminating in a limitation to the therapy. Also severe side effects of chemotherapy constitute a big problem of mortality percentage after anticancer treatment. This is the reason why in order to find good anticancer or antimetastatic agents, researchers investigate drugs which are used in the treatment of other diseases and are proved to be non-cytotoxic. As Sir
James Black (Nobel Laureate, 1924–2010) said: “The most fruitful basis for the discovery of a new drug is to start with an old drug.” Authors had an intention to gather and systemize the knowledge about anticancer activity of pentoxifylline - a very promising agent in subject of cancer treatment. Data from the National Cancer Institute provide information concerning the stage of investigations and what is expected to know about the examined compound in the nearest future.

**Metabolism of pentoxifylline**

Pentoxifylline, like caffeine, theobromine, theophylline, protheobromine and pentifiline belongs to a group of methylxanthines. From a chemical point of view, pentoxifylline is 1-(5-oxohexyl)-3, 7-dimethylxanthine with all the physicochemical properties coming from this origin. As regards metabolism of this drug, after absorption from the gastrointestinal tract pentoxifylline is bound slightly to plasma proteins and is spread evenly in the tissues of the body. It does not accumulate in the body. It is metabolized primarily in the liver and red blood cells, where it is formed to metabolite 1. The first five metabolites produced by reduction and oxidation of the oxohexyl substituent in position 1 of the xanthine ring. However, demethylation of pentoxifylline and metabolite 1 at position 7 leads to the formation of metabolites 6 and 7, respectively. The first five metabolites are 3,7-dimethylxanthines, the last two are 3-methylxanthines. Metabolites 1, 2, 3 and 5 have similar therapeutic efficacy as pentoxifylline (Wyska, 2010). (Metabolism of petoxifylline Fig. 1)
Fig. 1  Metabolism of pentoxifylline [1].
**Pentoxifylline and its cardiovascular action**

Pentoxifylline has hemorrhheologic properties and in this is way it influences cardiovascular system. This is the reason why it has been used in medicine for many years (NCI). The described compound inhibits phosphodiesterase, resulting in increased levels of cAMP in erythrocytes, endothelium and the surrounding tissues. This leads to vasodilation, improves erythrocyte flexibility and enhances blood flow. In addition, the increased level of cAMP in platelets inhibits platelet aggregation, which may contribute to a reduction in blood viscosity (NCI, 2012, Kostowski & Herman, 2003). Because of its influence on erythrocytes and blood flow, pentoxifylline is a drug used routinely in the clinical setting for circulatory diseases (Kostowski & Herman, 2003). It is used to treat intermittent claudication resulting from obstructed arteries in the limbs and vascular dementia (Wyska, 2010). Pentoxifylline improves blood flow through peripheral blood vessels and therefore helps with blood circulation in the arms and legs and the brain (hence its use in vascular dementia). The drug helps prevent strokes and can be used in managing sickle cell disease (Kostowski & Herman, 2003).

**Immunomodulating activity-Tumor Necrosis Factor**

Pentoxifylline possesses immunomodulating properties and the main target of its action in this case is Tumor Necrosis Factor (TNF). TNF plays an important role in the autoimmune response, in the case of overrelease it causes an allergic state. As regards cancer disease, TNF is responsible for cancer cachexia. Pentoxifylline inhibits production of TNF-α and interferon-γ while it induces Th2-like (T-helper 2) cytokine production, thereby inhibiting Th1- mediated (T-helper 1) inflammatory and autoimmune responses (NCI, 2012). Other data show that pentoxifylline and its metabolites poorly inhibit lipopolysaccharide- stimulated
TNF-α release by murine macrophages raw 264.7, and do not affect at all cell proliferation and upregulation of TNF-α-induced vascular cell adhesion molecule-1 in endothelioma cells h5v (Fantin et al., 2006). This indicates for need of further investigations.

The effectiveness and ability of pentoxifylline to inhibit anti-CD3 antibody-induced TNF production have been estimated in clinical studies in the National Cancer Institute as this is a therapeutically important process in cancer treatment. Patients also received there the anti-TNF therapy with ciprofloxacin and pentoxifylline during the peritransplant period. The National Cancer Institute evaluated the effect of pentoxifylline on TNF levels and quality of life in preterminal cancer patients. It was evaluated whether pentoxifylline improves the performance status and quality of life in patients with metastatic solid tumors. The fact if pentoxifylline decreases TNF levels in these patients and how the levels are correlated with the patients' symptoms was investigated (NCI, 2012). It means we can expect this information in nearest future and it will be known if it is possible to use pentoxifylline to relieve cachexia.

**Proapoptotic and antimetastatic properties**

In recent years, the anticancer properties of pentoxifylline have attracted a great deal of interest. Extensive research has been carried out to characterize the molecular mechanisms of its anticancer activity as well as its chemopreventive and chemotherapeutic potential. Pentoxifylline has been found to possess antineoplastic properties and those are very promising nowadays. It has been proved that it has proapoptotic and antimetastatic properties, but what is more important and promising is its augmenting role in the process of apoptosis. Antiangiogenic properties of pentoxifylline also play a very important role in the course of cancer treatment. Pentoxifylline has been shown to exhibit antimetastatic and antiangiogenic activities in B16F10 melanoma cells both *in vitro* as well as *in vivo* (Dua & Gude, 2006; Dua
& Gude, 2007; Dua & Gude, 2008).

It has been proved in MDA-MB-231 human breast cancer cells that pentoxifylline induces a G0-G1 cell-cycle arrest leading to apoptosis. Moreover, it affects adhesion to both the matrigel and collagen type-IV in a time and dose-dependent manner in this cell line. The pentoxifylline impedes the migration of MDA-MB-231 cells and also decreases the activities of both matrix metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9). MMP-2 and MMP-9 are the enzymes involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction and tissue remodelling, as well as in disease processes, such as arthritis and metastasis (Goel & Gude, 2011).

It has also been proved that pentoxifylline augments Tumor Necrosis Factor Apoptosis Induced Ligand (TRAIL)-mediated apoptosis. In cell lines HuT-78 and MyLa of cutaneous T cell lymphoma it acts through modulating extrinsic death receptors and intrinsic mitochondria dependent pathways. The compound augments TRAIL-mediated activation of caspase-8 and induces cleavage of Bid, although it alone cannot activate caspase-8. This is followed by cytochrome c release and subsequent activation of caspase-9 and caspase-3 and cleavage of poly(ADP ribose)polymerase (PARP). What is more, pentoxifylline and TRAIL combined treatment downregulates the expression of various antiapoptotic proteins including c-FLIP, Bcl-xl, cIAP-1, cIAP-2 and XIAP [9].

Pentoxifylline induces the expression of death receptors DR4 and DR5 on the cell surface of both cell types where c-Jun NH2-terminal kinase pathway plays an important role. Moreover, combined silencing of DR4 and DR5 by small interfering RNA abrogates the ability of pentoxifylline to induce TRAIL-mediated apoptosis (Gahlot et al., 2010).

The next important mechanism of action is pentoxifylline RhoGTPases inhibition. Pentoxifylline has also been found to inhibit migration by affecting RhoA and Rac1 GTPases-
the enzymes which induce B16F10 motility. Pentoxifylline, through its phosphodiesterase action, inhibits RhoGTPases and associated cellular organization in B16F10 melanoma and thus inhibits cell motility. This alkaloid derivative inhibits B16F10 melanoma lung homing by inhibiting F10 invasion, secretion of matrix metalloproteinase and adhesion to components of matrix. In this way pentoxifylline significantly inhibits F10 migration. Drug-mediated inhibition of the F10 migration process is connected with an increase in cellular cAMP levels. Pentoxifylline induces Protein Kinase A (PKA) activity and PKA inhibitor partly reversing their effects on F10 motility (Dua & Gude, 2008). Apoptosis induced by pentoxifylline in HuT-78 cells involves mitochondrial hyperpolarization, cytochrome c release, caspase-3 activation and PARP cleavage. Pentoxifylline treatment downregulates Bcl-xl and c-FLIP expression without affecting constitutive NF-κB but upregulates activator protein-1 (AP-1) in this cell line. Low concentration of pentoxifylline upregulates Fas and TRAIL expression in HuT-78 cells. The compound can act as a scavenger of reactive oxygen species (ROS). It could enhance Fas ligand (FasL) mediated killing in HuT-78 cells (Rishi et al., 2009). Pentoxifylline can trigger a series of events leading to apoptosis in HuT-78 cutaneous T cell lymphoma cells without affecting NF-κB- constitutive nuclear factor-κB, known as an important factor in the survival of HuT-78 cells (Rishi et al., 2009).

**Action of pentoxifylline in cases of multidrug resistance**

Multidrug resistance is a very serious and more and more common problem in cancer treatment. It thwarts chemotherapy and is the reason for poor prognosis. The main mechanism of multidrug resistance is an increase in drugs efflux by P-glycoprotein. Pentoxifylline is being considered in cases of multidrug resistance. The effects of pentoxifylline on P-gp-mediated multidrug resistance were evaluated in resistant to vincristine mouse leukemia 11210/vcr cells and it was found that compound downregulates P-gp protein expression.
Sensitization by pentoxifylline of the l1210/vcr cells line to vincristine was also examined. Sensitization occurred and correlation with the stimulation of apoptosis and proteolytic activation of both caspase-3 and caspase-9 were monitored. Higher release mmp-2, which could be attenuated by pentoxifylline, was found to be higher in resistant l1210/vcr cells than in l1210 cells (Docolomanský et al., 2005).

**Pentoxifylline and sensitization to extrinsic apoptosis**

Sensitization to drugs and radiation is sought nowadays and it plays an important role in cancer treatment since it allows reduction in a drug dose. This reduction means lower cytotoxicity and generally fewer side effects during chemotherapy. Pentoxifylline is a sensitizing agent to drugs and radiation, it makes therapeutically beneficial combinations.

**cisplatin**

Pentoxifylline sensitizes cervical cancer cells HeLa and SiHa cell lines infected with HPV types 16 and 18 to cisplatin-induced apoptosis and decreases the cisplatin-induced senescence in these cells via inhibition of the NF-κB signalling pathway. It diminishes expression of antiapoptotic proteins and the activation of caspases (Hernandez-Flores et al., 2011).

**perillyl alcohol**

*In vitro* experiments and phase I and II trials have shown that pentoxifylline sensitizes tumor cells to the antineoplastic action of perillyl alcohol (P-OH) which has antitumor effects. Pentoxifylline with P-OH induces loss of the mitochondrial membrane potential in the model cell line u937 *in vitro* (Gómez-Contreras et al., 2006).
Pentoxifylline also causes radiosensitization in human hepatocellular carcinoma cell line Hep3b possibly by the abrogation of G(2)/M arrest in Hep3b cells following radiation exposure (Wu & Liu 2006).

**adriamycin**

A combination of adriamycin and pentoxifylline increases apoptosis of HeLa and SiHa cervix cancer cells. Pentoxifylline elevates IκBα levels. Such sensitization is achieved through the upregulation of proapoptotic factors such as caspase and Bcl family gene expression. Pentoxifylline and pentoxifylline with adriamycin also decrease E6 and E7 expression in SiHa cells, but not in HeLa cells (Bravo-Cuellar et al., 2010).

**vitamin E**

Pentoxifylline in combination with vitamin E can reverse radiation-induced fibrosis as a radiation-induced side effect in women with breast cancer (Delanian et al., 2005; Magnusson et al., 2009).

**amifostine, ciprofloxacin, dexamethasone**

The amifostine, ciprofloxacin, dexamethasone and pentoxifylline combination may be beneficial in reversing cytopenias in the treatment of myelodysplastic syndrome and acute myeloid leukemia [Erikci et al., 2008; Barancik et al., 2012].

**Clinical trials of the National Cancer Institute**

Pentoxifylline is now in the phase of clinical trials in the National Cancer Institute at the National Health Institute in USA as regards its antitumor activities. Especially its combinations are currently intensively examined because of supportive activity of pentoxifylline in chemo- and radiotherapy. The results of the Institute will provide information whether pentoxifylline can be used to treat cancer on various levels.

The National Cancer Institute is estimating the antitumor activity of
cisplatin/pentoxifylline in patients with advanced, persistent or recurrent squamous cell carcinoma of the uterine cervix. The regimen-related toxicity of high-dose busulfan/cyclophosphamidere followed by allogeneic bone marrow rescue is also being assessed in advanced myeloma patients when the tumor necrosis factor was blockaded with ciprofloxacin/pentoxifylline/prednisone. The maximum tolerated dose of pentoxifylline with carboplatin in patients with advanced non-small cell lung cancer will be set. There is being determined the maximum tolerated dose of pentoxifylline administered with hydroxyurea during a course of cranial radiotherapy in patients with glioblastoma multiforme. The efficacy of amifostine, pentoxifylline, ciprofloxacin, and dexamethasone in suppressing the excessive apoptosis of hematopoietic cells in the bone marrow is being assessed in patients with myelodysplastic syndromes. They are trying to determine the maximum tolerated dose and pharmacokinetics of busulfan given with a fixed dose of cyclophosphamide along with antitumor ciprofloxacin and pentoxifylline in patients with breast cancer. The Institute is evaluating healing of radiation-related soft tissue necrosis treated with pentoxifylline and best supportive care vs. best supportive care only in patients irradiated for head and neck, skin, vulvar, vaginal, cervical, or anal cancer. They are evaluating activity of suramin plus either thiotepa/pentoxifylline or doxorubicin in patients with metastatic prostate carcinoma refractory to endocrine therapy and suramin. There is being determined optimal dose of prophylactic pentoxifylline that can be administered with high-dose interleukin-2 (IL-2) in patients with selected refractory solid tumors and lymphoma, and it is being assessed whether granulocyte-macrophage colony stimulating factor and pentoxifylline reduce the incidence and severity of posttransplant mortality and morbidity from granulocytopenia and veno-occlusive disease in patients with lymphoid or myeloid malignancies. Pentoxifylline is also taken into consideration as a supportive agent. The researchers study whether pentoxifylline is effective in maintaining weight in patients undergoing chemotherapy for metastatic cancer
Conclusions

The compound is worth studying because of an increasing range of its activities. Antineoplastic and proapoptotic properties of pentoxifylline have been proved, although it seems to be the most useful in a combined treatment of cancer. In conclusion, the data are consistent that pentoxifylline can induce apoptosis by engaging many pathways, so it can be considered a new chemotherapeutic.

Furthermore, when pentoxifylline is combined with other drugs, it can sensitize the apoptosis pathways, which is very beneficial. This fact offers hope of decreasing dosage and thus decreasing toxicity of the treatment.

Pentoxifylline is very promising as a supportive agent in chemo- and radiotherapy. After chemo- and radiotherapy courses with pentoxifylline, patients are in a better condition as they are protected against radiation and cytotoxicity. Pentoxifylline prevents radiation-induced fibrosis and others radiation-induced side effects in women with breast cancer. What is more, if it was used as a protector during radiotherapy and chemotherapy, it would also protect against veno-occlusive disease- a severe and mortal side effect of anticancer treatment. Pentoxifylline possesses hemorrhheologic properties, so it should be considered in cases with a risk of veno-occlusive disease. Influence of pentoxifylline on TNF should also be explained as the next target for this compound is the improvement of the oncological patient's condition. An agent which reduces cachexia is really needed, and it is possible that pentoxifylline can improve the quality of the oncological patients' life since it is effective in maintaining weight in these patients. What is important, this also concerns patients undergoing chemotherapy for metastatic cancer.

Finally, further studies are required to understand the mechanisms by which
pentoxifylline influences apoptosis. This knowledge is necessary to recognize the full spectrum of the anticancer activity of pentoxifylline and is needed for the development of new anticancer treatments. What is more important, further clinical trials are required to confirm beneficial influence on organs during chemo- and radiotherapy.

**Declaration of Interest**

The authors report no declarations of interest.

**References**


