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REVIEW ARTICLE

Potential Use of Pentoxifylline in Cancer Therapy

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Abstract: ***Background***: Pentoxifylline (PTX) is a drug commonly used in the treatment of intermittent claudication. However, numerous research groups report that PTX also may potentially be used in the anticancer therapy following one of the main trends in the nowadays medicine – combined anticancer therapy.

Scope of Review: The review concentrates on the reports revealing the potential use of PTX in cancer treatment.

Major Conclusion: PTX is described to possess several properties which may be exploited in cancer treatment. The drug reportedly not only has anticancer activity itself, but also increases cancer cells susceptibility to radiation therapy and, additionally, reduces long-term side effects of this therapy. Furthermore, numerous research groups report that PTX may increase the anticancer potential of commonly used anticancer drugs such as cisplatin or doxorubicin as well as reduce side effects of these drugs.

Significance: PTX should be considered as a potential drug in the combined anticancer therapy.

Keywords: Radiosensitization, drug interactions, methylxanthines, anticancer drugs, chemotherapy, drug toxicity.

1. INTRODUCTION

Diseases of affluence become increasingly prevailing in the modern society, especially in the developed countries. One of the most common and deadliest diseases of affluence is cancer (the other being heart diseases). Extensive research on both cancer diagnostics and treatment methods contributed to the tremendous increase in the survival rate (69% in the 2003-2009 and 49% in the 1975-1979 periods in the United States), American Cancer Society – Facts and Figures). The data for other countries show an even greater increase (*e.g.* 24% in 1970s and 50% in 2000s in the United Kingdom, British Cancer Society – Cancer Statistics). Nevertheless, even 1 out of 4 deaths in the US may be attributed to cancer, which means that about 650,000 people die yearly due to cancer in the US only (American Cancer Society – Facts and Figures). Such an enormous death toll stimulates further, even more exhaustive, research aiming at the reduction of the massive figures describing cancer mortality.

Nowadays, there are two main trends in cancer research. Scientists concentrate either on developing completely new drugs and targeted therapies or on improving existing therapies in order to increase their effectiveness and selectivity. Both approaches have their pros and cons, as, despite increasing number of therapies against specific cancer type, the variability and diversity of the disease makes the other second approach necessary.

The latter approach uses established anticancer drugs combined with biologically active compounds that may be used to reduce side effects of the drug and, hopefully, improve the efficacy of the therapy. It bases either on use new compounds, possibly possessing anticancer ability by themselves (*e.g.* fullerene C_{60}), or exploration of known substances to find the novel application of compounds already used in medicine or pharmacology (*e.g.* methylxanthines). In this work, we describe the potential to use of one of methylxanthines – pentoxifylline in the combined chemotherapy.

2. PENTOXIFYLLINE

Pentoxifylline (PTX, 1-(5-oxyohexyl)-3,7-dimethylxanthine) is a semi-synthetic methylxanthine derivative. It was approved as a drug for intermittent claudication in 1972 in Europe and in 1985 in the US [1, 2]. This drug was extensively analyzed afterward to assess all its properties and uses in medicine. The results revealed numerous potential treatments that may involve PTX. PTX, as other methylxanthines, has the potential to inhibit phosphodiestrase activity, interfere with both calcium pumps activity [3] and DNA

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repair processes [4], however, the cardiac effects of PTX are significantly reduced in comparison to other methylxanthine – caffeine [5]. Interestingly, even in case of caffeine induced fever the symptoms were observed after consumption of either caffeine or theophylline, but not PTX [6]. Another potential use of the drug is connected with the reduction of TNFα production [7, 8] as well as glycemia levels in diabetic patients [8]. At the same time, PTX is reported to reduce the expression of transduction vectors of HIV reducing its virelemia [9] and mediate inflammation processes as well as attenuate endothelial functions in infected patients [10]. PTX is also described as a potential chemopreventive agent as it forms mixed stacking aggregates with aromatic mutagens such as ICR-191 [11] and heterocyclic aromatic amines [12, 13]. Finally, PTX is reported to have prospective use in the treatment of surgical patients after intervention. Researchers observe the reduction of time required for wound healing process [14] as well as attenuation of cytokine response during surgery and postoperative need for painkillers such as morphine [15] after administration of PTX. Although the side effects of PTX therapy are relatively low, they have to be mentioned. Even the prolonged use of the drug is connected mainly with problems with digestive system such as indigestion, nausea or vomiting, however, the use of PTX may also lead to dizziness, insomnia, headaches or angina [1, 16-18]. Nevertheless, it has to be noted that PTX may decrease plasma fibrinogen levels leading to bleedings in patients with platelet dysfunction [18-20].

2.1. Pentoxifylline and Cancer Growth

Among the other modes of action, PTX is reported to have anticancer activity. As early as in 1991 Edward and MacKie described the reduction of growth rate of B16F10 melanoma cell line connected with increased melanin synthesis as well as enhanced lung metastasis of this cancer line by PTX (pretreatment of tumor cells with 250 μg/ml dose of the drug). The authors suggested that change in the integrins expression profile may be behind observed phenomenon [21]. However, in 1996 Gude *et al.* showed, on the same cell line, that lower doses of PTX have reversed the prometastatic effects of PTX with growth reduction still observed by authors. In their work, the authors refer to direct interactions of PTX with the cancer cells receptors as well as adhesion molecules that can be found on the lung endothelium [22]. The following research by Gude *et al.* revealed that PTX increases expression of metalloproteinase MMP2/galatoinase A and reduces expression of metalloproteinase MMP9/ galatoinase B [23]. These enzymes are responsible for the migration of metastatic cells through the extracellular matrix. A similar change in their expression patterns was observed by Reis *et al.* for HL-60 leukemia cell line [24]. PTX is also reported to reduce tumor angiogenesis, which may be a factor in the drugs antiproliferative activity [25].

Subsequent research by Shukla and Gude revealed that some of antimetastatic properties of PTX may by connected reduced glutathione concentration in the melanoma cells [26]. The reduction of intracellular glutathione in the cancer cells is connected with increased membrane permeability, while high glutathione concentration in the melanoma cells is connected with metastasis to the liver [27]. The results obtained by Alexander *et al.* confirm previous findings and suggest that PTX may alter the phenotype of melanoma cells [28]. The authors also showed that PTX promotes lysis of cancer cells by lymphocytes, however, the effect is cancer type dependent as a similar experiment conducted on low metastatic lung cancer cell line Hs294T showed the opposite results [28]. Research of Dua *et al.* indicated that PTX may affect morphology of the melanoma cells inducing "cAMP phenotype", which may also affect their motility [29]. However, what is even more important, in these authors research PTX induced melanin secretion by the B16F10 cell line [29], which is considered marker of melanoma cells differentiation [30]. What is more research of Dua *et al.* confirmed metastasis inhibition by affecting MMP2 and MMP9 metalloproteinases [29]. Following research of the same group confirmed their conclusion of PTX affecting the motility of B16F10 *via* induction of "cAMP phenotype". In the same work activation of protein kinase A by PTX is proposed as next factor that may affect melanoma cells motility and hence their migration [31]. Furthermore, the results presented in the aforementioned work indicate that PTX may affect both Rho GTPases activity and its localization. Inhibition of Rho GTPases and the change of their localization to cytoplasm only (from membrane and cytoplasm localization) changes actin organization inside the B16F10 cells which might be the main factor in the reduction of their metastatic potential by PTX [31]. Research conducted by Ratheesh *et al.* confirmed previous findings on PTX influence on melanoma B16F10 metastasis to lungs and, additionally, provided insight into the modulation of integrin expression by PTX. The authors also assessed the impact of PTX on the expression of protein kinase C and proposed that inhibition of this enzyme, responsible for integrin transport, might be the phenomenon responsible for modulation of integrin expression [32]. These findings were subsequently confirmed by the following research of the same group [33]. Research conducted by Kamran and Gude on the melanoma cell line A375 showed similar inhibition of migration and adhesion of cancer cells by PTX with the mechanism being inhibition of metalloproteinases MMP2 and MMP9 possibly by inhibition of STAT3 signaling pathway [34]. Furthermore, authors observed inhibition of melanoma cell growth by pentoxifylline in the doses of 3 mM and above [34]. The authors subsequently assessed the hypothesis of PTX inhibiting STAT3 signaling pathway in their next work [35]. The research revealed that PTX downregulates the STAT3 pathway [35], which is reported to play a crucial role in the cancer proliferation and survival [36]. PTX downregulates STAT3 pathway *via* inhibition of kinases pJAK1 and pJAK2 as well as promotion of pSHP2 phosphatase. What is worth mentioning, the PTX selectively inhibits STAT3 signaling pathway, while not affecting STAT1 signaling pathway [35], which shares 72% homology with STAT3 and is described as tumor growth suppressor [37]. In spite of promising research on antimelanoma properties of PTX Sant *et al*. analyzed potential ways of enhancing PTX activity, reporting 20% enhancement of PTX anticancer activity after its encapsulation in liposomes [38].

All the promising results described above were obtained on the melanoma cell lines. However, research was also conducted on other cancer cell lines. Goel and Gude, in their series of three research papers, analyzed influence of PTX on

the human breast cancer. In the first work the authors analyzed influence of the PTX on the MDA-MB-231 cell line. Their findings indicate both cytostatic and antimetastatic potential of the drug. The modulation of the MAPK kinases is proposed as a mechanism behind cytostatic potential of PTX, while mechanisms affecting cancer metastasis are reported to be more complex [39]. In their work researchers analyzed some of the factors described as antimetastatic in melanoma and found most of them affect breast cancer metastasis as well, namely, the factors were: changes in the cell morphology and integrins expression pattern as well as modulation of metalloproteinases expression [39]. The second work of these authors concentrates on the influence of PTX on focal adhesion kinase (FAK) and Rho GTPase signaling pathways as well as cell cycle modulation in breast cancer [40]. The first signaling pathway is connected with tumorogensesis and cell proliferation *via* modulation of ERK and MAPK kinases as well as Akt pathway. PTX downregulates FAK and, therefore, increases number of cells undergoing apoptosis. The modulation of Rho GTPase is, similarly to the melanoma, responsible in changes in cell morphology and disruption of cytoskeletal functions, therefore it reduces cancer cells potential to metastasis. Finally, the authors reported stage G1/S blockage of cell cycle in cancer cells which leads to increased apoptosis of the MDA-MB-231 cancer cell line [40]. In their last work Goel and Gude concentrated on the influence of the PTX on the adhesion of chosen breast cancer line indicating reduced adhesion of the cancer cells to numerous surfaces such as matrigel, collagen type IV, fibronectin or laminin [41]. The mechanisms behind observed antimetastatic action are modulation of integrins expression on the MDA-MB-231 breast cancer cells by decreasing α5, β1 and β3 integrins expression [41]. These integrins are reported to play crucial role in breast cancer adhesion to the fibronectin [42]. On the other hand, changes in the expression of the α2 and β5 integrins were negligible [41]. Therefore, the authors suggest that antimetastatic potential of PTX might be connected with regulation of cancer cell-extracellular matrix adhesion [41]. Recently, Castellanos-Esparza *et al.* confirmed PTX anticancer activity against MDA-MB-231 breast cancer cell line. Additionally, the authors observed synergistic effects of PTX and simvastin (anti-hypercholestrolemic agent) and connected this phenomenon with ERK1/2 and Akt activation together with NFκB inactivation [43]. Similar results were obtained by Napolitano *et al.* who observed inhibition of NFκB/p65 signaling pathway together with reduction of Bcl-2 protein expression in chronic leukocytic leukemia [44]. The data obtained by Wang *et al.* on HepG2 cancer cell line [45] confirm activation of ERK1/2 and MAPK pathway [40, 43] and cell cycle arrest [40], however, unlike Goel and Gude, Wang *et al.* identify G0/G1 stage as the stage when arrest takes place [45]. Furthermore, Grinberg-Bleyer *et al.* assessed in more detail influence of PTX on NFκB activity and observed that the drug directly interacts with c-Rel subunit of NFκB and affects expression patters of c-Rel dependent transcription only [46]. Finally, Hernandez-Flores observed cytotoxicity of PTX against human cervix carcinoma lines HeLa and SiHa connected with lack of such toxicity towards HaCaT keratinocytes [47].

Amirkhosravi *et al.* reported cytostatic effects of PTX against Neuro2a neuroblastoma and HT29 human colon carcinoma. The authors observed also reduced adhesion of Neuro2a cell line to fibronectin coated surface. However, when Neuro2a cells were injected into the lungs of mice 70% of animals in the treated groups developed pulmonary nodules, while none in control group [48]. Interestingly, Stefankova *et al.* during research on L1210 lymphoma cell line found that PTX is more toxic to drug-resistant L1210/Vdr cell line than to nonresistant cell line [49]. *In vivo* research conducted by Bałan *et al.* revealed that PTX slows L-1 sarcoma growth and reduces tumor volume [50]. On the other hand, Lazarczyk *et al.* analysis of PTX influence on the adenocarcinoma led to completely different results showing a negative effect of PTX on cancer treatment. The authors observed PTX induced inhibition of immunological system response to cancer through affecting splenocytes cytotoxic activity and infiltration of peritumoral tissue by leukocytes [51]. In their subsequent work, the same group investigated effects of PTX on the development of mouse C-26 adenocarcinoma. The results were opposite to the reports on PTX influence on melanoma – tumor proliferation and metastasis to the liver were enhanced [52]. In their final work, the authors compared PTX influence on melanoma and adenosarcinoma metastasis to lungs. The results were cell line dependent – melanoma metastasis was inhibited, while adenocarcinoma promoted [53].

Presented reports indicate that PTX is cytostatic to cancer cell lines *via* modulation of MAPK kinases, especially by affecting STAT signaling pathways. Additionally, PTX can influence cancer metastasis by affecting integrins expression pattern and changing its morphology, as well as NFκB signaling pathway. However, PTX exact role has to be further analyzed, especially on the cancer cell lines other than melanoma, which was the prevalent cell line in the analyzed reports. Moreover, Lazarczyk and his group, in their works [51-53], showed that the effects may be cell line dependent with results obtained for adenocarcinoma being completely different from the data for melanoma. Finally, two interesting issues have to be addressed: the effects of PTX in higher concentration and explanation for better efficacy of PTX on the drug resistant leukemia cell line than on the nonresistant cell line.

2.2. Pentoxifylline and Radiotherapy

Other extensively analyzed properties of PTX are connected with radiotherapy. In their work in 1989 Dion *et al.* described effects of PTX on radiation induced soft tissue necrosis and late radiation injuries in mice [54]. As radiotherapy is one of the main therapies available for cancer these results led basis for further research not only on mitigation of radiotherapy side effects but also on radiosensitization of cancer cells by PTX. Lee *et al.* in their works analyzed radiosensitizing potential of PTX alone or combined with nicotinamide [55, 56], the compound with described potential to increase radiotherapy effectiveness [57]. In their first work authors analyzed effects of both PTX alone and combined with nicotinamide on the radiosensitivity of the murine fibrosarcoma FSaII *in vivo*. Their results indicate that PTX increases radiosensitivity of the chosen cancer and combination of PTX with nicotinamide is more effective

than either of the compounds alone. The proposed mechanism of observed phenomenon bases on the increased oxidization of cancer cells [55]. In their second work authors analyzed this mechanism more deeply. Their findings suggest that PTX combined with nicotinamide increases oxidization of the cancer cells by increasing blood flow through tumor blood capillaries and by increasing the amount of oxygen released from hemoglobin by decreasing their affinity [56]. The tumor perfusion problem was studied in more detail by Bennewith and Durand. In their work they concentrated on tumor radiosensitizing agents that can penetrate inside of the tumor despite its poor blood circulation. The authors indicated that PTX (in dose 50 mg kg^{-1}) increases tumor perfusion by more than 100% 15 mins after administration, therefore, increasing amount of drug reaching interior of tumor and its oxidization [58]. Li *et al*. in their work proposed other mechanism to be responsible for colon and cervix cancer radiosensitization. Namely, PTX, as other methylxanthines, inhibits G_2 phase checkpoint during mitosis, therefore, the cells have less time to repair DNA damage induced by radiotherapy, and as the result undergo apoptosis. What is more, the authors suggested that this effect is more pronounced in cells lacking p53 function, caused by either mutation or HPV infection [59]. Similar conclusions were drawn by Bohm *et al.* who analyzed a few methylxanthine derivatives on radiotherapy of melanoma and squamous carcinoma and pointed out PTX as most promising agent. The authors confirmed results of Li *et al.* showing that PTX reduces time of G_2/M cell cycle arrest, therefore, increasing number of apoptotic cancer cells. Additionally, the authors reported higher radiosensitizing potential of PTX in p53 deprived cells when compared to p53 wild type [60], finding corresponding to results obtained by Li *et al.* [59]. All these results were further confirmed by Theron *et al.*, who also partially attributed radiosensitization of cancer cells by PTX to its potential to disrupt mechanisms of DNA damage repair. However, this phenomenon is observed in cell lines with both functional and nonfunctional p53 protein [61].

The results of Binder and Bohm indicate that cell cycle disruption by PTX after radiotherapy may be attributed to the increasing phosphorylation of histone H3 [62]. Strunz *et al.* in their research analyzed further disruption of cell cycle inducted by PTX. The authors showed that PTX indirectly activates $p34^{cdc2}$ kinase and promotes abrogation of G_2/M cell cycle checkpoint [63]. Danielsson *et al.* further analyzed PTX influence on cell cycle and DNA repair mechanisms confirming findings on abrogation of G_2/M cell cycle checkpoint and disruption of DNA repair mechanisms. The most pronounced influence was observed on mechanisms responsible for repairing double-strand breaks in DNA - one of the main types of DNA damage induced by radiotherapy [64]. Kinuya *et al.* in their work came up to conclusions connecting both modes of PTX action mentioned above – the authors claim that increased tumor radiosensitivity should be attributed to better tumor oxidization induced by PTX as well as cell cycle disruption [65]. On the other hand, some research groups suggested that PTX radiosensitizes glioma [66] and hepatoma cells [67, 68] only by disruption of cell cycle and DNA repair mechanisms, but not *via* tumor oxidization [66-68]. On the other hand, Zywietz *et al.* suggested opposite mechanism and the crucial role of increased tumor oxidization, with only marginal effects of disruption of cell cycle visible only in p53 mutant cell lines [69].

Moreover, Dion *et al.* in spite of their promising results on PTX reducing radiation burns and soft tissue necrosis on mice [54] started to further analyze PTX influence on radiation injuries. The authors conducted a preliminary study on human with late radiation soft tissue necrosis. Their results are promising as PTX induced significant healing to the late radiation injuries and, what is more, time between the injury and start of the PTX treatment was much longer than the time required to significant improvement of patients condition [70]. Radiation therapy is also the trigger of radiation induced tissue fibrosis, which can develop as late as 10 years after radiation therapy [71]. However, PTX combined with vitamin E (vitamin E, tocopherol) not only relives the pain [72] and reduces the symptoms of the radiation induced fibrosis but also leads to return to normal tissue [71]. In their next work Delanian *et al.* observed reduction of fibroses in 23 out of 28 areas of radiation induced fibrosis induced by PTX and vitamin E therapy. The authors suggested that the treatment consists of two stages: PTX inhibits extracellular matrix production and enhances collagenase activity, that is followed by scavenging of free oxygen radicals by vitamin E. The therapeutic effect is only visible when both compounds are administered [73]. These findings were further confirmed by another research group, who also shown that significant effects of the therapy are visible after no less than 6 months [74].

Okunieff *et al.* performed series of experiments to assess mechanisms of PTX action in case of healing radiation induced fibrosis. However, the number of mechanisms PTX may exploit in the process is so high that the authors were unable to conclusively indicate only one of them. Two most probable are improvement in the blood flow in the tissue reducing hypoxia and inhibition of platelet derived growth factor and IL-1β [75]. The latter is reported to promote radiation induced fibrosis in the lungs [76]. Aygenc *et al.* analyzed emergence of acute and late skin changes induced by radiotherapy on two groups of patients: untreated and with prophylactic PTX treatment. Results indicate no effects of prophylactic PTX administration on acute skin changes, however, the authors observed reduced incidence and severity of late radiation induced changes, namely radiation induced fibrosis [77]. Simultaneously, Hille *et al.* analyzed effects of PTX administered in combination with vitamin E on the radiation proctitis/enteritis. The results indicate similar healing effects as observed in case of radiation induced fibrosis, with the minimal time required to observe beneficial effects set on 6-12 months. However, the research was conducted on the low number of patients [78]. In the same time, Ozturk *et al.* analyzed influence of PTX on radiation induced injuries in lungs after radiation therapy of lung or breast carcinomas. Their results indicate that PTX dose of 1200 mg per day significantly reduces occurrence of both symptomatic lung injuries (from 30% patients in the placebo group to 5% in the treated group) and radiologic changes in lungs (from 75% in the placebo group to 45% in the treated group) [79]. Similar effects were observed by Kaidar-Person in patients treated for breast cancer [80].

Subsequently, Williamson *et al.*, analyzed influence of PTX and vitamin E in the adverse radiation effects after radiotherapy of brain tumors. The results indicate that regimen of PTX combined with vitamin E may effectively reduce radiotherapy side effects in brain [81]. What is more, the authors analyzed possible mechanisms of action of PTX confirming and expanding the conclusions of Okunieff *et al.* [75]. Williamson *et al.* showed that PTX reduces expression of not only IL-1β but also vascular endothelial growth factor. These expression changes inhibit migration of fibroblast to the blood vessels, reduce radiation induced vascular necrosis, prevent radiation induced changes in vascular morphology, and inhibit integrins expression, increasing local blood flow as a result [81]. In case of vitamin E the results described by the authors are in agreement with the results of Delanian *et al.* vitamin E scavenges free oxygen radicals [73]. What is more, Liu *et al.* showed that, except for being free radical scavenger, vitamin E downregulates TGF-β1 expression, therefore, reducing severity of radiation induced fibrosis [82]. In 2009 Magnusson *et al.* published report from phase II clinical trial for prevention of radiation side effects with combined PTX and vitamin E therapy. Published results indicate that preventive administration of PTX + vitamin E therapy reduces arm swelling, however, authors did not observe reduction in radiation induced fibrosis occurrence and severity [83]. Finally, Hayashi *et al.* decided to assess the impact of PTX and vitamin E combined therapy on osteaoradionecrosis – common side effect of brain or neck tumor radiotherapy. The results were promising with observed regression of osteoradionecrosis in as much as 84% of treated patients [84]. The treatment is reported to be especially effective in case of jaw osteoradionecrosis and in patients requiring dental extractions [85-87]. In 2002 Delanian and Lefaix proposed further modification to regimen of PTX combined with vitamin E (tocopherol) - addition of clodronate [88], which is now generation bisphosphonate used in the treatment of osteoporosis [89]. Clodronate acts *via* stimulation of osteoblast inducing direct formation of the bone [90]. The new regimen produced striking results of complete reversion of osteoradionecrosis and associated radiation induced fibrosis [88, 91]. The results were further confirmed during research on the group of 54 patients [92]. However, Gothard *et al.* analyzed effects of regimen of PTX combined with vitamin E on lymphoedema and radiation fibrosis in the patients after breast surgery and radiotherapy. Their findings showed no beneficial effects healing of radiation induced fibrosis and lymphoedema [93]. The same group conducted similar analysis in patients after pelvic radiotherapy. In this case the authors observed beneficial effects of the therapy in some patients, but the results remained inconclusive [94]. Shoma *et al.* analyzed different formulation of combined therapy for radiation induced burns - the authors substituted vitamin E with honey. The results were also promising showing reduction of radiation induced burns severity up to complete recovery induced by PTX and honey combined therapy. What is more honey ointment is reported to reduce pain of burns and improve quality of life of the patient [95].

All the results presented demonstrate that PTX has the potential to increase tumor radiosensitivity, however, the mechanism of this phenomenon is still being disputed. The authors discuss whether disruption of the cell cycle and DNA repair mechanisms [60-62] or increased tumor oxidization [69] are the mechanisms most responsible for the observed effects. The majority of works negate the importance of the latter, however, Kinuya *et al.* suggest that both mechanisms play an equally important role in the observed phenomenon [65]. Therefore, further research is required to answer arising question. The radiosintetizing properties of PTX are reportedly connected with its potential to reduce side effects of the radiotherapy, namely radiation-induced fibrosis and burns, osteoradionecrosis and side effects on brain blood system. However, some authors report no effects of PTX in the treatment of radiation induced fibrosis [93, 93]. Futhermore, one of the recent work concentrates on the intensification of PTX side effects, mainly nausea, and relatively weak improvement in the patient well-being [96]. Most works focus on long-term side effects of radiotherapy, and the only study on the prophylactic use of PTX before and during radiotherapy reported no positive effects of such treatment [77]. Bearing these results in mind together with small samples used in all studies analyzed here the positive effects of PTX on the treatment of radiotherapy require further confirmation on the larger group of patients.

2.3. Pentoxifylline and Chemotherapy

Numerous reports describe PTX potential to enhance the action of anticancer antibiotics. In the late 1980s and beginning of 1990s Fingert *et al.* and Boike *et al.* in their research evaluated the potential of methylxanthines in thiotepa therapy of bladder carcinoma [97] and cisplatin therapy of ovarian and cervical cancer [98]. The authors pointed out PTX as the most promising agent with the great potential to enhance chemotherapy without side effects associated with high doses of caffeine [97, 98]. Fingert *et al.* showed that combination of PTX with anticancer agent thiotepa results in the enhanced anticancer activity of the drug without increasing its side effects [99]. Dezube *et al.* conducted phase I trial of combined therapy with thiotepa and PTX as early as in 1990. Their results indicate a reduction of side effects connected with cancer chemotherapy as well as an increase in anticancer activity of the drug in some cases [100].

In 1991 Schiano *et al.* analyzed the potential of PTX to overcome cisplatin resistance in the ovarian cancer cell line BG-1. The results are promising and, furthermore, authors analyzed potential mechanisms of PTX action attributing PTX activity to direct interactions with ADP-ribosyltransferase - enzyme directly involved in the repair processes - rather that abrogation of cell cycle checkpoints [101]. However, Fan *et al.* analyzed the influence of PTX on cisplatin action in MCF-7 breast cancer cell line with mutated p53 gene, revealing that PTX increases the effectivity of cisplatin by affecting G_2 checkpoint in these cells [102]. Furthermore, Stewart *et al.* in their pilot study on overcoming multidrug resistance to carboplatin, suggested a combination of numerous compounds including PTX [103]. During that time research on combining PTX with doxorubicin was also conducted and Chitnis *et al.* reported PTX potential to sensitize murine doxorubicin resistant P388 leukemia cell subline to vincristine [104]. Subsequently, the same research group analyzed the influence of PTX on doxorubicin resistance of chronic myeloid leukemia. In the case of this cancer cell line, PTX halved doxorubicin dose required to inhibit cancer growth.

The authors observed higher accumulation of doxorubicin in the cancer cells and reduced efflux of the drug and, therefore, suggested that observed phenomenon may be connected with direct interactions of PTX with phosphoglycoprotein-P [105], one of the proteins involved in the multidrug resistance of cancer cells [106]. The results and stated hypothesis were further confirmed by next research published by the same group [107]. Sadzuka *et al.* observed corresponding effects of PTX on doxorubicin, namely reduced dose required for therapeutic effects and reduced efflux from cancer cells, in their research on Ehrlich ascites carcinoma [108].

Stefankova *et al.* analyzed potential sensitization of multidrug-resistant L1210/Vdr cell line to vincristine by pentoxifylline, caffeine and theophylline. Interestingly, the authors observed sensitization of cancer cells to vincristine only by PTX, but not by other methylxanthines [49]. Therefore, this effect cannot be attributed to characteristic common to all methylxanthines but as suggested by Viladkar *et al.* [105] direct interactions of PTX with phosphoglycoprotein-P [49]. This research group continued research on the subject revealed that PTX not only helps to overcome multidrug resistance in L1210/Vdr cancer cells but also reduces the time required by cancer cells to enter programmed cell death pathway [109]. This phenomenon may possibly reduce the potential to develop such resistance by cancer cells [109]. Subsequently, Binder *et al.* in their research assessed the influence of PTX on cytotoxic activity of daunorubicin, cisplatin, and melphalan. The authors observed an increase in the cytotoxicity of the analyzed anticancer drugs by PTX and attributed it to the same phenomenon as the increase of cancer radiosensitivity - abrogation of G_2/M cell cycle checkpoint. Additionally, the authors suggested other, auxiliary, mechanisms of PTX action - inhibition of DNA repair mechanisms and interference with P-glycoprotein mediated efflux of anticancer drugs [110]. Research of Drobna *et al.* indicated that PTX may not only interact directly with P-glycoprotein, what was described before [49, 105] but also reduce its concentration in the cancer cells by downregulation of *mdr1* gene expression [111]. The following research of this research group indicated that reduction of anticancer drug efflux by PTX is not based on competition for the binding site on the P-glycoprotein, but rather on the binding of PTX to different site on the P-glycoprotein molecule and altering its structure, thus rendering it impossible to bind to the anticancer drug such as vincristine or doxorubicin [112]. The work of Barancik *et al.* [113] confirms results on both reduction of P-glycoprotein concentration, which was suggested to be reduced by PTX *via* downregulation of *mdr1* gene [111] and binding to the P-glycoprotein molecules themselves [49, 104, 112]. Interestingly, the authors attributed overcoming of L1210/Vdr cancer cell line resistance to vincristine also to the inhibition of metalloproteinases release [113], a mechanism which is reportedly also involved in the anticancer activity of PTX itself [23, 29, 34].

Lerma-Diaz *et al.* also studied the influence of PTX on anticancer activity of doxorubicin and observed increase in doxorubicin activity in both murine L-5178Y and human U937 tumor cell lines. Furthermore, authors investigated the observed phenomenon and proposed two potential mechanisms of PTX action. First, PTX modulates inhibition of transcription factor NF-κB translocation to nucleus *via* stabilization of its natural inhibitor IκBα. This effect is mediated by inhibition of phosphorylation of IκBα on Ser32, preventing IκBα degradation and stabilizing IκBα complex with NF-κB in cytoplasm. Second mechanism, analyzed in series of experiments with caspase inhibitors, is apoptosis *via* the caspase cascade, affecting mainly caspase 3 and caspase 9. Interestingly, the authors suggested that alternative apoptosis pathway is involved - *via* caspase X, resulting in Δψm loss and release of apoptogenic factors from mitochondria [114]. Effects similar to the latter were observed by Gomez-Contreras *et al.* in the research where U937 cancer cells were treated with peril alcohol and PTX. The authors observed changes in the expression patterns of antiapoptotic Bax and Bcl-2 proteins and loss of Δψm resulting in apoptosis [115]. The same research group analyzed this issue deeper in their subsequent research revealing that PTX combined with proteasome inhibitor MG132 downregulates NF-κB and antiapoptotic proteins Bax and Bcl-2 and induces Δψm loss together with activation of caspase cascade resulting in increased apoptosis in U937 leukemia cells [116]. Other research of the same group on the PTX influence on doxorubicin resistance of cervix cancer cell lines HeLa and SiHa confirmed that PTX both reduces efflux of doxorubicin from cancer cells and promotes apoptosis of the cancer cells [117]. The authors observed increased expression of proapoptotic proteins such as caspase3, caspase 9, puma, noxa, and Diablo. Upregulation of *p53* gene was also observed, however the authors didn't register elevated levels of p53 protein [117] confirming the previous hypothesis that the apoptotic pathway induced by PTX and doxorubicin is p53 independent and follow the caspase cascade mechanism [104, 117]. At the same time the authors noted no senescence promotion in cells treated by PTX and doxorubicin [117]. Hernandez-Flores *et al.* analyzed the same cancer lines, namely HeLa and SiHa, treated with combination of PTX and cisplatin. In this case authors also observed increased apoptotic potential of PTX and cispaltin compared to drug alone and reduced senescence of cancer cells. The first phenomenon is connected not only to increased expression of proteins playing crucial role in the caspase cascade, namely caspase 3 and caspase 9, but also to reduction of NF-κB expression and activation of survival pathway. The latter is also connected with reduction of cancer cells senescence together with reduction of ERK1/2 phosphorylation and downregulation of *survivin* gene. Interestingly the authors did not observe increased apoptosis in the HaCaT keratinocyte cell line [47]. Downregulation of NF-κB by PTX and its positive effects on anticancer therapy were further confirmed in the research of Gonzalez-Ramella *et al.* The authors analyzed influence of PTX on the treatment of acute lymphoblastic leukemia with prednisone, revealing not only downregulation of NF-κB but also inhibition of transcription factor STAT3 and downregulation of genes from the Bcl family [118]. The effects of combining doxorubicin with PTX were further assessed by Goel *et al.* on the MDA-MB-231 breast cancer cell line and HT-1080 fibrosarcoma. The authors noted increase of apoptosis observed when cells were administered doxorubicin and PTX compared to doxorubicin alone. Furthermore, the expression profile of metalloproteinase 2 and 9 was altered, however, the authors attributed these effects to PTX, dismissing any effects of doxorubicin or synergy of PTX with doxorubicin in this aspect. *In vivo* experiments revealed that

combining PTX with doxorubicin resulted in delay of cancer growth in nude mice at lower doses of both drugs used [119]. Furthermore, Nidhyanandan *et al.* analyzed combination therapy of PTX and histone deacetylase inhibitors MS275 and vorinostat on panel of cancer cell lines (namely, breast cancer cell lines MDA-MB-231 and MCF-7, colon carcinoma HCT116, and prostate adenocarcinoma PC3). Again the synergistic effects were observed in case all of the analyzed cell lines and apoptosis *via* the caspase cascade together with cell cycle arrest and blocking of VEGF-A signaling pathway were noted [120, 121]. One of the newest studies describes effects of PTX administered together with steroid prednisone in the treatment of acute lymphoblastic leukemia. The authors observed increase of cancer cells apoptosis during steroid window and connected this phenomenon with deubiquitination of RIPK1 protein (activator of NFκB) and downregulation of antiapoptotic protein BCL2 [122]. What is more, Kim *et al.* observed 2-fold improved distribution of doxorubicin and gemcitabine by PTX in pancreatic tumor xenografts [123].

The protective effects of PTX against side-effects of anticancer therapy were also analyzed. Piosik *et al.* assessed influence of methylxanthines including PTX on another important issue connected with chemotherapy are local side effects such as tissue necrosis or extravasations. In their research authors described potential of methylxanthines to form mixed stacking aggregates with anticancer drugs such as doxorubicin, daunomycin and mitoxantrone, calculating mixed association constant values for these interactions. The authors hypothesized that observed phenomenon may lead to local decrease of anticancer drug concentration and, therefore, reduction of side effects observed at the injection site [124]. The following research of the same group resulted in the more complex analysis of PTX influence on the doxorubicin binding to DNA and development of novel mathematical tools required by the process [125] and subsequent analysis of doxorubicin derivative – idarubicin [126]. Authors also analyzed influence of PTX on the mutagenic activity of doxorubicin in the Ames test and observed significant reduction of the latter by PTX in the concentration-dependent manner. Interestingly, the MTT tests on the HaCaT, MCF-7 and MEL-Juso (keratinocyte, breast cancer and melanoma cell lines, respectively) revealed protective effect only in case of keratinocytes [127]. This phenomenon confirms results obtained by Hernandez-Flores *et al.* who observed no increased apoptosis in the HaCaT cell line after administration of doxorubicin and PTX [47]. All these results indicate protective effects of PTX against side effects of doxorubicin therapy that may occur at the anticancer drug administration site. Furthermore, the authors indicated that the huge difference in the half-life of PTX and anticancer drugs analyzed (4h to 140h, respectively) should not negatively affect anticancer activity of antineoplastic drugs [124-127]. At the same time, research of Kim *et al.* demonstrated reduction of cisplatin renal toxicity by PTX. The authors attributed observed phenomenon to potential of PTX to restore blood flow in kidneys by inhibition of TNFα induced apoptosis [128]. Similar effects were observed for doxorubicin induced renal disease -PTX administration improved condition of the patients and reduced number of renal cells undergoing TNFα mediated apoptosis [129]. These results are supported by corresponding data obtained by Saad *et al.* for other methylxanthine derivative - theophylline and cisplatin [130]. What is more, Zang *et al.* observed reduction of myocardial fibrosis induced by doxorubicin treatment, when the antineoplastic drug was administered together with PTX. The authors attributed observed phenomenon mainly to inhibition of TGF-β, mainly downregulation of *TGF-β1* gene expression [131]. Finally, Fallahzadeh *et al.* assessed influence of PTX on cisplatin induced testicular toxicity in rats. The authors observed partial reduction of the cisplatin toxicity in rats pretreated with PTX for 2 weeks establishing the most effective dose at 75 mg/kg body weight, however, the side effects of cisplatin treatment differed depending on the dose of PTX administered. Therefore, further research is required [132].

All the groups agree that administration of PTX together or shortly before each chemotherapy dose increases the anticancer activity of the analyzed drugs. Mechanisms observed are in agreement with those observed for the PTX cytotoxic activity (interactions with STAT signaling pathway) and radiotherapy enhancement (cell cycle modulation). However, it still needs to be answered whether observed effects are synergistic or additive only. Another important issue is the effect of such combined regimen on metastasis as, in spite of results suggesting cancer cell line dependency of PTX action, it cannot be neglected that in some cell lines PTX may promote metastatic processes. PTX is reported not only to increase anticancer activity of the antineoplastic drugs, but also to reduce both local (at administration site) and systemic (*e.g.* kidney or heart) side effects of the chemotherapy. The efficiency of PTX and anticancer drugs combination therapy in the prolonged timeframe should also be assessed.

CONCLUSION

Numerous reports presented in this work indicate the potential role of PTX in combination anticancer therapy. According to the literature published, PTX may not only enhance antineoplastic drugs activity, but also has an anticancer activity, which makes it even more potent in the combined chemotherapy. Furthermore, direct interactions of PTX with aromatic anticancer drugs are reported to reduce both systemic and local side effects of the chemotherapy and, additionally, protect normal cells without interfering with anticancer activity of the drug. Finally, PTX exhibits potential to both enhance radiotherapy efficiency and reduce long-term side effects of radiation. All these characteristics make PTX a promising candidate to be further assessed as a putative component of combined anticancer treatment. These findings can be exploited by clinicians all around the world - However, the questions stated in this work cannot remain unanswered. Particularly, the potential dependency of PTX anticancer activity on cancer cell line needs to be evaluated. Furthermore, the problems of studies with contradictory results and low sample sizes in the case of PTX influence on radiotherapy should be solved. Last but not the least, the prolonged effects of PTX on anticancer drugs efficiency should be established.

Nonetheless, all the findings presented in this work may be of huge impact on the everyday clinical practice. The regimen of PTX combined therapy with vitamin E (toco-

pherol) and, possibly, clodronate can be introduced to reduce side effects of anticancer radiotherapy, even few years after the radiation treatment. Additionally, use of PTX together with classic anticancer drug such as anthracycline antibiotics, cisplatin or mitoxantrone in the combined chemotherapy regimen will, reportedly, not only reduce both systemic and local side effects of the anticancer drugs but also increase the efficiency of the therapy, especially against resistant cancer types. Therefore, animal research and clinical trials should be launched immediately to test and, hopefully, introduce this new regimen into the clinics.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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G.G. analyzed literature and wrote the manuscript. A.W. reviewed the manuscript and J.P. designed the study and reviewed the manuscript.

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