CHAPTER 2

Cyclopentenyl Cytosine (CPEC): An Overview of Its In Vitro and In Vivo Activity

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ABSTRACT

The experimental cytotoxic drug cyclopentenyl cytosine (CPEC) is an analogue of cytidine. Besides its antiviral effect, its potential use in the treatment of cancer has become an important area of research. CPEC is activated by intracellular phosphorylation ultimately forming its metabolite CPEC-TP. CPEC-TP is a non competitive inhibitor of cytidine-5'-triphosphate synthetase (CTP-synthetase), an important enzyme in the formation of CTP. Studies have shown that cancer cells have a high CTP synthetase activity, thus making CTP synthetase an interesting target for chemotherapy. CPEC has been preclinically studied in different malignancy models. In vitro results on leukemia show activity in the nanomolar range on several cell lines. However in vivo results are conflicting and the findings vary from increase in life span over 100% to only limited effectiveness. Interesting results have been obtained in colorectal and neuroblastoma cells. In several neuroblastoma cell lines incubation with CPEC in combination with cytarabine or gemcitabine has resulted in increased cell death compared to incubation with only one of the agents.

CPEC has been studied in a phase I trial in patients with solid tumors. In five of 26 patients unexplained cardiotoxicity (extreme hypotension) occurred.

In this overview, it is demonstrated that CPEC has an anti-cancer effect in several tumor models and might be a potentially useful drug in anticancer treatment.

Keywords: Cyclopentenyl cytosine, CPEC, cancer, leukemia, cardiotoxicity
INTRODUCTION

Nucleotides are the phosphorylated forms of nucleosides and the mature precursors of DNA and RNA. Because of their important role in DNA and RNA synthesis and thus in cell survival, nucleotides appear to be important targets in anticancer therapy. Indeed, several anticancer drugs, such as methotrexate or 5-fluorouracil, exert their action by interfering with nucleotide biosynthesis. Moreover, as cancer cells show an increased demand for nucleotides when compared to healthy cells, they may preferentially be targeted by these anticancer drugs. Nucleosides contain either a purine (adenosine or guanosine) or a pyrimidine base (cytidine, thymidine or uridine) [1]. The least abundant nucleoside in the cell is cytidine [2]. Cytidine 5'-triphosphate (CTP) can either be formed from cytidine 5'-di- and monophosphate (CDP, CMP) or from UTP (uridine 5'-triphosphate). The formation of CTP from UTP is catalyzed by the enzyme cytidine 5'-triphosphate synthetase (CTP-synthetase). Fig. (1)

Figure 1 Pyrimidine synthesis

The pyrimidine (deoxy) ribonucleotide synthesis is shown. Pyrimidine nucleotides can either be formed by de novo synthesis starting with glutamine or from uridine and cytidine. ATP: adenosine 5'-triphosphate; UTP: uridine 5'-triphosphate; UDP: uridine 5'-diphosphate; UMP: uridine 5'-monophosphate; CTP: cytidine 5'-triphosphate; CDP: cytidine 5'-diphosphate, CMP: cytidine 5'-monophosphate; dCDP: 2'-deoxycytidine 5'-diphosphate, dCTP: 2'-deoxycytidine 5'-triphosphate.

The numbers represent the enzymes catalyzing the conversions:
1: NDP kinase; 2: NMP kinase; 3: uridine/cytidine kinase; 4: CTP synthetase; 5: (deoxy) CMP deaminase; 6: (deoxy) cytidine deaminase; 7: ribonucleotide reductase; 8: deoxy cytidine kinase.
Thus, a cell can have two different sources for CTP: CTP can be provided by the salvage pathway by phosphorylation of cytidine or by 'de novo' synthesis out of UTP. An increased activity of CTP-synthetase has been demonstrated in several malignant cell types such as hepatic carcinoma, renal cell carcinoma, acute lymphocytic leukemia and lymphoma [3-6]. CTP synthetase might therefore be an attractive target for growth inhibition of malignant cells by depletion of CTP pools. Depletion of CTP pools will lead to a reduction of proliferation of cells. Furthermore, as depletion of the CTP ribonucleotide pool also leads to a depletion of the cytidine deoxyribonucleotide (dCTP) pool, the balance in the ribonucleotide amount in cells will be disturbed and other deoxyribonucleotides than dCTP can be misincorporated during DNA synthesis, triggering apoptosis [7, 8].

The cytotoxic drug cyclopentenyl cytosine (CPEC) was designed in 1979 based on the biologically active and toxic nucleoside neplanocin A that was found in fermentation broth. Out of several purine and pyrimidine analogues of neplanocin A, CPEC was found to be the most biologically active compound with regard to antiviral activity and activity against murine leukemias and human tumor xenografts [9]. CPEC is an analogue of cytidine in which the ribose moiety is substituted by a carbocyclic sugar. Fig. (2)

![Chemical structure of CPEC](image)

As cytidine is hydrophilic, passive diffusion across cell membranes is not likely and nucleoside transporters are necessary for uptake of CPEC in cells. The equilibrative nucleoside transporters (ENTs) ENT1 and ENT2 both seem to be involved. Whether other nucleoside transporters such as the concentrative nucleoside transporter (CNT) are also involved is not clear [10]. The multidrug resistance proteins 4 and 5 (MRP4 and MRP5) also are suggested to be involved in nucleoside transport [11]. However, in human cells the transport of other nucleoside analogs such as gemcitabine and cytarabine seems to be predominantly regulated by ENT and CNT [12,
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After the facilitated diffusion through the cellular membrane, CPEC is phosphorylated [14]. CPEC-monophosphate is formed by uridine cytidine kinase. Nucleoside monophosphate (NMP) and nucleoside diphosphate kinase (NDP) are responsible for the further phosphorylation ultimately leading to CPEC triphosphate (CPEC-TP). Fig. (3)

![Figure 3 Metabolism and proposed mechanism of action of CPEC](image)

CPEC can be either cleared as unchanged drug or deaminated to its metabolite CPEU by the enzyme cytidine deaminase (5). CPEC-MP: CPEC-monophosphate; CPEC-DP: CPEC-diphosphosphate; CPEC-TP: CPEC-triphosphate

The numbers represent the enzymes catalyzing the conversions:
1: uridine/cytidine kinase; 2: NMP kinase; 3: NDP kinase; 4: CTP synthetase; 5: cytidine deaminase

After incubation with CPEC, Moyer et al found strong inhibition of the formation of [3H]-CTP from [3H]-uridine in L1210 cells. This suggested inhibition of CTP synthetase by CPEC [15]. In K562 cells CPEC also induced erythroid differentiation in presence of p38 MAP kinase activity [10]. CPEC-TP was found to be mainly responsible for this effect as μM-range concentrations of CPEC-TP were able to inhibit CTP synthetase, whereas CPEC, CPEC-MP and CPEC-DP showed no inhibition at all or only at much higher concentrations [16]. Cyclopentenyl uridine (CPEU), the deamination product of CPEC, seems to be the major metabolite of CPEC with almost no cytotoxic effects [14, 17].

The observed preclinical effects of CPEC suggest a potential use as an anti-cancer agent. In this review an overview of both the preclinical and early clinical studies undertaken with CPEC will be given. Studies were selected by Medline search using the keywords [cyclopentenyl cytosine], [cyclopentenylcytosine] and [CPEC].
PRECLINICAL ACTIVITY OF CPEC

In vitro antiviral activity

Like several other pyrimidine nucleoside analogues, CPEC has both antiviral and anti-tumor effects. The mechanism of action of the antiviral effect is believed to be based on the CTP depletion caused by CPEC. Apparently CTP synthetase interacts as a host cell enzyme that may be used as a target enzyme for antiviral agents. In in vitro assays, CPEC showed antiviral activity against a broad range of viruses (e.g. herpes simplex, polio, rhino, influenza, yellow fever, West Nile) at a wide range of concentrations. An IC50 of 0.02 μg/ml (80 nM) was observed for vaccinia viruses [18]. This concentration is comparable to concentrations at which anti-tumor effect is observed. However, most of the viruses were inhibited at concentration of 0.1 μg/ml (400 nM) and higher.

The in vitro assays for antiviral activity were conducted on resting confluent cells whereas exponentially growing cells were used for the anti-tumor assays. Exponentially proliferating cells seem to preferentially use the ‘de novo’ synthesis of CTP (involving CTP synthetase) thereby making them more sensitive to CPEC.

Antiviral activity has not yet been established in animal models. Whether it is possible to create an antiviral effect without toxic effects on rapidly growing cells is therefore not clear yet [18-22].

Activity in malignancies

LEUKEMIA, IN VITRO STUDIES

In MOLT-4 lymphoblasts CPEC concentrations between 20 nM (72 hr incubation) and 75 nM (16 hr incubation) were able to reduce proliferation rates by 50% [14]. In the human promyelocytic leukemia cell line HL-60, DNA synthesis was almost completely inhibited after 24 hrs incubation with 30 nM CPEC. At this concentration RNA synthesis was less reduced (approximately 30% reduction) [23]. In cells from pediatric patients with acute lymphocytic and acute non-lymphocytic leukemia, incubation with CPEC caused a dose dependent depletion of CTP [24, 25]. CPEC was also used in combination with cytarabine and analogues. Cytarabine must be phosphorylated before it can be incorporated into DNA and exert its cytotoxic effect. The rate limiting enzyme in this process is deoxycytidine kinase (dCK). The activity of dCK is regulated and can therefore be inhibited by deoxycytidine-triphosphate (dCTP). De novo synthesis of dCTP occurs by reduction of cytidine 5'-diphosphate to 2'-deoxycytidine 5'-diphosphate by ribonucleotide reductase and subsequent phosphorylation to dCTP by nucleoside 5'-diphosphate kinase. Depletion of CTP pools leads to a decrease in dCTP and could have a positive influence on incorporation of cytarabine. Incorporation of cytarabine into DNA was increased with by 41% in a human T-lymphoblastic cell
line (MOLT-3) after preincubation with CPEC (100nM), followed by incubation of cytarabine (2nM) [26]. Similar results were obtained with the deoxycytidine analogue 5-aza-2’-deoxycytidine (DAC) and gemcitabine in combination with CPEC in HL60 cells [27, 28] and MOLT-3 cells [28].

LEUKEMIA, IN VIVO STUDIES

Moyer et al inoculated mice with the lymphoid leukemia cell line L1210 (1x10⁵ cells). Several dose regimens were applied; from 10-50 mg/kg as a single dose to 1-6 mg/kg/day for 5 days and 1 mg/kg/day for 9 days. All mice, including those receiving saline, died within 20 days after inoculation. An increase in life span (ILS) of 111-122% was observed after 9 days of treatment with 1 mg/kg CPEC. The other regimens were either too toxic (> 3 mg/kg for 5 consecutive days) or ineffective (single dose up to 50 mg/kg) [15]. These results correspond with other experiments in L1210 inoculated mice [29]. Although with a broader range in ILS (73-129%), increase in life span was also reported for mice inoculated with P388 lymphocytic leukemia [15]. Combination treatment of the palmitate derivative of cytarabine and CPEC in mice inoculated with L1210 cells (with a subpopulation resistant to cytarabine), resulted in an increase in lifespan when compared to single treatment with the palmitate derivative only. However, since toxicity of the combination was more severe than while using monotherapy, the maximum tolerated dose (MTD) of palmitate cytarabine as a single agent was not achieved. When the MTD in both regimens was compared there were no longer significant differences in survival [30].

NEUROBLASTOMA

At concentrations similar to those at which anti-leukemic activity was observed, CPEC was also active on SK-N-BE(2)-C neuroblastoma cells [7, 31]. Moreover, coincubation of CPEC (50-250 nM) and cytarabine (37.5-500 nM) increased the cytotoxic effects of cytarabine [32]. Preincubation of CPEC (100 nM) followed by the deoxycytidine analogue gemcitabine (50 nM), also resulted in increased cell death for 13 of the 15 neuroblastoma cell lines when compared to a set up in which incubation with only gemcitabine took place [33].

BRAIN TUMORS

CPEC has demonstrated in vitro activity against human glioblastoma cells [34]. However, CPEC shows relatively poor penetration of the blood brain barrier. In mice inoculated intracerebrally with leukemic L1210 cells intraperitoneal administration of CPEC was less effective than in mice inoculated intraperitoneally or subcutaneously with L1210 [18]. It can be concluded that CPEC does not appear to be a suitable agent to be used in brain tumors. However, the poor penetration of CPEC intracerebrally might be overcome by direct intratumoral administration of the drug. In one study CPEC (200 μM by continuous infusion in 4 weeks) was directly infused into brain gliosarcomas in rats [35]. Rats treated with CPEC survived 32 days versus 25 days for rats treated with saline (p<0.0001). In tumor tissue CTP was depleted to a much greater extent.
than in the adjacent tissues, indicating that exposure to CPEC was restricted to the infused area. The absence of systemic exposure might indicate that intratumoral administration results in less toxic effects. Whether intratumoral administration of CPEC is feasible in humans needs to be investigated further.

COLORECTAL CARCINOMA

Growth inhibitory effects of CPEC have been demonstrated in four different human colorectal cell lines (HCT 116, SNU-C4, NCI-H630 and HT-29) [36, 37]. The IC50 values vary between 10 and 60 nM after 72 hours of incubation (HCT 116, SNU-C4 and NCI-H630) and 460 nM after 24 hours of incubation (HT-29). For an in vivo study, mice were inoculated with HT-29 cells. Although CPEC treatment did not fully halt tumor growth, it was shown that the increase was only one third of the growth measured in controls [38]. Combination treatment of CPEC with cisplatin was examined in vitro and in vivo (athymic mice) using HT-29 cells [39]. Cisplatin treatment alone did not result in significant tumor reduction; this is in line with clinical data indicating limited activity of cisplatin in colorectal carcinoma as a single agent [40]. However, when cisplatin (4 mg/kg Q7Dx3) was combined with CPEC (1.5 mg/kg, QDx9) tumor volume was reduced to 16% of the volume in the control group. Treatment with CPEC alone resulted in a reduction of 40%. However, when treatment was stopped, tumor growth was detected again, indicating a cytostatic and not cytocidal effect [39].

IN VITRO RESISTANCE

Since in clinical oncology drug resistance is a frequent cause of treatment failure, attempts have been made to investigate CPEC resistance in vitro in MOLT-4 lymphoblasts and L1210 leukemic cells [41,42]. In the resistant MOLT-4 lymphoblasts, CPEC-TP was formed 10-100 fold lower than in the wild type cell line. Resistance could be partly explained by a decreased activity of the enzyme uridine-cytidine kinase which catalyses the first phosphorylation step of CPEC. However, this was not the only possible explanation as concentrations of CPEC-TP that were cytotoxic in the wild type cell line, were found not cytotoxic in the resistant cell line and high CTP levels were found in the resistant cells. Therefore it could be concluded that there was another mechanism at work and it is believed that this could be a change in CTP-synthetase activity [42, 43]. This second mechanism was confirmed in leukemic cells, where an increased activity of CTP-synthetase was found in the resistant cells without a change in uridine-cytidine kinase [42].

An increased activity of the enzyme that is responsible for the deamination of CPEC (cytidine deaminase, CDD, Fig.3) to its metabolite CPEU could be a third cause of resistance. By deaminating cytosine nucleosides and analogs, CDD prevents the accumulation of the intracellular active triphosphates. Overexpression of CDD has been associated with protection of cells from
cytarabine and gemcitabine [44]. A fourth hypothetic mechanism might be found in the transport over the cellular membrane. Huang et al showed that CPEC diffusion is facilitated by ENT1 and ENT2 [10]. Changes in these transporters might influence the uptake of CPEC in the cell. Nitric oxide has been able to reduce ENT1 promotor activity in human fetal endothelium [45] and during hypoxia ENT1 function seems to be repressed, making hypoxic tumors potentially susceptible for reducing CPEC uptake [46]. It is not clear whether other transporters involved in nucleoside transport such as CNT and MRP4 and MRP5 are involved in CPEC transport. If CPEC transport would not be mediated by other nucleoside transporters, tumors predominantly expressing CNT might be resistant to CPEC. However, there are little data as yet about nucleoside transporter expression among tumors. What is clear however, is that leukemia cells seem to have both an ENT and a CNT transporter function [47].

Although it is unclear whether in vitro created resistance is a good model for future in vivo resistance, the results described here might be a useful tool in understanding resistance in vivo.

MODULATION OF CYTOTOXIC EFFECT

The deamination product of CPEC, CPEU was found to protect cells against the cytotoxic effects of CPEC [17]. Coincubation of a 100-fold higher concentration of CPEU (50 μM) with CPEC (0.5 μM) resulted in 50% survival of cells, whereas only 10% survived with 0.5 μM CPEC alone. Addition of the CPEU after incubation of CPEC diminished the increase in survival. An inhibition of uridine-cytidine kinase was suggested to be responsible for the ‘rescue’ by CPEU. This might result in decreased concentrations of CPEC-TP as uridine-cytidine kinase is necessary for the first phosphorylation step of CPEC. Clinical implications of this effect are not to be expected as CPEU levels in humans did not exceed those of CPEC [48]. Cytidine might be a more useful modulator of CPEC activity. In vitro experiments in leukemic and colorectal cells have shown an increase in survival even after delayed administration of cytidine to CPEC treated cells [14, 37]. Combination treatment of CPEC and cytidine in mice inoculated with L1210 cells resulted in less toxicity without significant changes in increase in lifespan [29]. Competition for transmembrane transport and phosphorylation might be responsible for the observed effects. It was suggested that by delaying the administration of cytidine a first rapid effect of CPEC could be induced, followed by a rescue of toxic effects of cytidine [14].

In neuroblastoma cells retinoic acid attenuated the effects of CPEC and resulted in a 5 to 20 fold increase of IC50 of CPEC. As both agents show activity against neuroblastoma, this might have consequences for future combined therapy regimens [49].
Chapter 2

PHARMACOKINETICS

Animal

Zaharko et al. studied the pharmacokinetics of CPEC in mice, rats and beagle dogs. The plasma concentration was best described by a three compartment model consisting of a central compartment (extracellular fluid) and two cellular compartments. After distribution a rapid first elimination phase was observed followed by a long terminal half-life which probably is caused by the retention of CPEC as CPEC-TP and subsequent slow release of CPEC from CPEC-TP by phosphatases. CPEC was mainly cleared into urine unchanged for all different species studied [50]. In contrast to these data, clearance of CPEC in nonhuman primates occurred primary by deamination by cytidine deaminase to the inactive metabolite CPEU. Only 20% of the total dose was excreted as an unchanged drug. The deamination resulted in a lower total exposure of CPEC (expressed by a lower AUC) in monkeys compared to an equivalent dose of CPEC in rodents. CPEC was rapidly eliminated with a terminal half life of 20 to 60 minutes. Two hours after a single dose of CPEC, CPEU levels exceeded CPEC levels more than 40 fold. However, after continuous infusion steady state concentrations of CPEU varied no more than 4 times the CPEC levels, suggesting a saturable metabolism. The differences between rodents and nonhuman primates may be explained by the activity of cytidine deaminase. Rats have an almost non-existent cytidine deaminase, whereas high levels can be found in nonhuman primates [51]. Results from these studies have been used to determine the dose of CPEC to be used in clinical trials.

Human

Data from two patients that received an intravenous test dose of 24 mg/m² showed two phases of rapid elimination of CPEC from the plasma (half-lives 8 and 100 minutes respectively). CPEC could still be detected 24 hrs after the end of the infusion, suggesting the existence of a third phase resulting in a long terminal elimination half-life. Measurements from 26 patients receiving a 24 hrs continuous infusion of CPEC confirmed these results. During the 24 hrs-infusions the steady state plasma levels increased linearly with increasing doses and steady state was achieved after approximately 12 hrs of infusion. Plasma concentrations of CPEU were below CPEC levels [48]. These pharmacokinetic data are in line with the results from preclinical studies in rodents [50]. Humans are reported to have less cytidine deaminase than nonhuman primates [51]. Deamination therefore seems to be not as important in clearance as it is in the case of nonhuman primates and CPEC is mainly eliminated as an unchanged drug in the urine.
TOXICOLOGY

Animal

Toxicity of CPEC seems to be dose and schedule related. Mice can tolerate single doses of CPEC up to 50 mg/kg without showing any signs of toxicity [15]. However, more than 2 mg/kg for at least 9 days results in weight loss [15, 29]. Tolerability of CPEC also seems to differ among the different species. No toxicity of CPEC was detected in rats treated with 2 mg/kg/day for a period of four weeks [35]. The difference in tolerability between species was confirmed by other experiments showing a more toxic effect of CPEC on mice than on rats [52]. The high cytidine levels or almost absent levels of cytidine deaminase in rats are thought to account for these differences. Single doses of CPEC in beagle dogs (3-40 mg/kg) resulted in oral lesions and a decrease in body weight. Bone marrow and gastro-intestinal epithelium were also affected [53].

Human

In a phase I study in 26 patients with solid tumors granulocytopenia and thrombocytopenia were reported as dose limiting toxicities in 2 of 3 patients during the first 3 weeks after a 24-hour infusion of CPEC at a dose of 5.9 mg/m² per hr, whereas non dose limiting were vomiting, mucositis and diarrhea. The majority of patients had colorectal cancer and most of them were heavily pretreated with chemo- and/or radiotherapy. All but one patient had documented disease progression prior to entering this study. The median time to treatment failure was > 3 months in 11 patients (42%), which is compatible with an active antitumor agent. However, the most severe adverse effect was a severe hypotension which occurred in 5 patients at the lower dose levels of 3.5 and 4.7 mg/m² per hr and resulted in death in two of them. None of the patients experiencing the hypotension was dehydrated. Hypotension occurred 24 to 48 hours after the end of infusion and seemed to be dose related. No hypotensive episodes or other important toxicity occurred at doses equal or below 2.5 mg/m² per hr. Laboratory results from the hypotensive patients showed a pattern consistent with hypoperfusion (hypoxemia, increased creatinine and metabolic acidosis). The echocardiograms showed left ventricular contraction but no signs of pericardial effusion. Post mortem examination on one of the two deceased patients revealed subendocardial necrosis and minimal pericardial effusion. From the other patient it was known that there was no prior cardiac history [48]. The mechanism of these hypotensive episodes was not clarified. Between those patients that did experience hypotension and those that did not there were no differences in the CPEC-CPEU ratio. Moreover, inhibition of CTP synthase activity seemed to be similar for all patients. These findings suggested that there were no differences in uptake or excretion between the patients. Influence of CPEC on cardiolipin metabolism (a major phospholipid in the heart) [54, 55] or a preference in the cardiomyocytes for CTP synthesis by the salvage pathway via CTP synthetase, were proposed mechanisms.
CONCLUSION AND PLACE IN THERAPY

The mechanism of action of CPEC is supposed to involve inhibition of the enzyme CTP-synthetase. As a high activity of this enzyme has been observed in several malignancies [3-6], CTP-synthetase seems to be an interesting target for a wide range of tumors.

The effects of CPEC have been studied most extensively in leukemia. Current therapy for leukemia has improved survival, however, e.g. ALL is still associated with a poor prognosis and new agents are warranted. Therapy with CPEC in humans with solid tumors resulted in hematotoxic side effects [48], suggesting that leukemic cells might be sensitive to CPEC. Indeed several preclinical studies show anti-leukemic activity of CPEC. Moreover, it might be worthwhile to investigate the use of CPEC in combination with other drugs for the treatment of ALL, like cytarabine. Other promising areas might be colorectal carcinoma and neuroblastoma. For colorectal carcinoma addition of CPEC to currently used therapy combinations (e.g. oxaliplatin with fluorouracil and the VEGF inhibitor bevacizumab) could be of interest. As the use of CPEC in neuroblastoma has only been studied in vitro, testing the drug in an animal model will be necessary to confirm the in vitro data. Based on the in vitro data it might be interesting to study the effect of CPEC on neuroblastoma in combination with other drugs, like gemcitabine.

The observed cardiotoxic side effects in the Phase I trial remain a point of concern and care should be taken if the drug is to be administrated in future clinical trials. As the toxicity seemed to be dose related, a restriction in the maximum administrated dose will have to be considered in these trials. Moreover, close monitoring of plasma levels will be necessary to check whether the administrated dose does not lead to plasma levels at which cardiotoxicity occurred in the Phase I trial.

The reviewed data in this manuscript illustrate an anti-cancer effect of CPEC in several tumor models and suggest that CPEC might be a potential drug in anticancer treatment. Further study is needed, however, until now only preclinical data on efficacy are available and it is as yet unclear whether the same anti-cancer effect of CPEC can be reached in humans.
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