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Review

Therapeutic potential of the biscoclaurine alkaloid, cepharanthine, for a range of clinical conditions

Moshe Rogosnitzky[1], Rachel Danks[2]

[1]MedInsight Research Institute, P.O. Box 386, Telz Stone, 90840, Israel

[2]MedInsight Research Institute, Island West, Steep, Hampshire, GU32 1AE, United Kingdom

Correspondence: Moshe Rogosnitzky, e-mail: moshe@medinsight.org

Abstract:
Cepharanthine (CEP) is a naturally occurring alkaloid extracted from the plant *Stephania cepharantha* Hayata. It has been widely used in Japan for more than 40 years to treat a wide variety of acute and chronic diseases. CEP inhibits tumor necrosis factor (TNF)-α-mediated NFκB stimulation, plasma membrane lipid peroxidation and platelet aggregation and suppresses cytokine production. It has also been shown to scavenge free radicals and to have a protective effect against some of the responses mediated by pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1ß and IL6. CEP has successfully been used to treat a diverse range of medical conditions, including radiation-induced leukopenia, idiopathic thrombocytopenic purpura, alopecia areata, alopecia pityrodes, venomous snakebites, xerostomia, sarcoidosis, refractory anemia and various cancer-related conditions. No safety issues have been observed with CEP, and side effects are very rarely reported.

Key words:
cepharanthine, leukopenia, alopecia, snakebites, multiple myeloma, sarcoidosis, anemia, cancer

Abbreviations: CEP – cepharanthine, HIV – human immunodeficiency virus, ITP – idiopathic thrombocytopenic purpura, MDR – multi-drug resistance, NK – natural killer, NO – nitric oxide, SADBE – squaric acid dibutylester, TNF – tumor necrosis factor

Introduction

Cepharanthine (CEP) is a natural alkaloid extracted from the plant *Stephania cepharantha* Hayata, a herb native to the woods of southern Formosa, which is now in Taiwan [40]. It is approved by the Japanese Ministry of Health for the treatment of radiation-induced leukopenia, alopecia areata and alopecia pityrodes. It has been used in Japan for more than 40 years to treat a wide variety of acute and chronic diseases [15, 24].

CEP belongs to a class of compounds known as biscoclaurine alkaloids, which are defined by the presence of a 1-benzylisoquinoline moiety on their alkyl chain. Alkaloids of this class have long attracted the attention of pharmacologists and clinicians because of their resemblance to polypeptides, their relationship to natural products of similar composition and their physiological actions [40].

CEP is an ether-soluble, optically active, non-phenolic, amorphous tertiary base that can only be crystallized from benzene. It is cationic and amphipathic and has

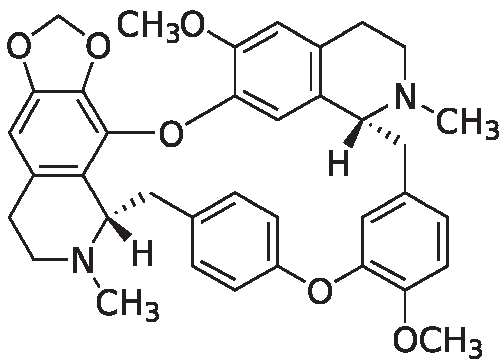

Fig. 1. Chemical structure of cepharanthine (CEP)

been reported to decrease the fluidity of various biological membranes [47]. The structure of CEP (Fig. 1) was first determined by Kondo and Keimatsu in 1938 [Kondo, Keimatsu, Ber, 1938, 71, 2553]. Attempts have been made to synthesize CEP chemically, but these have so far been unsuccessful [40].

CEP is available in tablet and powder form for oral administration [Cepharanthine package insert, 2008] and also in an injectable form. Once absorbed, it is mainly distributed to the liver, spleen, kidney and lung. In healthy adult males, the time to maximum serum concentration (t_{max}) following oral administration of a 10 to 60 mg dose is between 1.1 and 2.5 h and is approximately 1.2 ± 0.3 h following administration of 120 mg [Cepharanthine package insert, 2008]. The 48 h cumulative urinary excretion rate of 120 mg of CEP in healthy adult males is 1.4 ± 0.3% [Cepharanthine package insert, 2008].

CEP appears to provide clinical benefits in an astonishing array of medical conditions. Conditions that have been reported to benefit from CEP therapy include radiation-induced leukopenia [4, 55, 61, 68, 69, 74] idiopathic thrombocytopenic purpura [32, 50], alopecia areata [43], alopecia pityrodes [Cepharanthine package insert, 2008], venomous snakebites and some aspects of cancer [25, 53, 72]. It has also been suggested that CEP has benefits in the management of HIV [6, 57, 58] and malaria [7, 71], and may act as an antitumor [3, 9, 10, 13, 20, 23, 26, 56, 60, 79] and anti-allergic agent [2, 12, 35, 36, 38, 49]. It has also been reported to reverse multi-drug resistance [1, 11, 13, 27, 31, 44, 46, 48, 57, 67], and potentiate chemotherapy [8, 26, 54] and display anti-inflammatory effects [16].

Although the mechanisms underlying the action of CEP are not fully understood, they are believed to be heterogeneous due to CEP's efficacy among a broad range of conditions [29]. Several *in vivo* and *in vitro* studies have demonstrated that CEP inhibits tumor necrosis factor (TNF)-α-mediated NFκB stimulation, plasma membrane lipid peroxidation [12, 46, 65] and platelet aggregation [22, 37, 62, 63], and suppresses cytokine production. It has also been shown to scavenge free radicals [33, 34] and to have a protective effect against some of the responses mediated by pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1β and IL6 [45].

This paper is a review of the principal preclinical and clinical data available relating to the use of CEP for a range of conditions. Because CEP is currently only commercially distributed in Japan, reports showing its clinical efficacy are almost exclusively restricted to Japan. Furthermore, as CEP is not patent-protected, it does not enjoy the level of commitment and funding available to patented therapies from companies with a vested interest in their success. Consequently, no structured research program has been conducted to examine the benefits of this agent, and the current clinical data available are not as comprehensive as one would wish for an agent with such apparent potential.

Preclinical findings

A considerable body of preclinical data is available in the literature, which includes both *in vitro* and *in vivo* findings that support the therapeutic potential of CEP for treating a wide variety of clinical conditions. The following sections present a review of the most pertinent preclinical studies available that examine the potential benefits of CEP in the fields of antitumor activity, potentiation of chemotherapy, multi-drug resistance, induction and suppression of apoptosis, allergies and inhibition of histamine release, inhibition of platelet aggregation, septic shock, HIV, malaria and immunomodulatory responses.

Antitumor activity

CEP appears to limit tumor growth in a number of ways, including through direct cytotoxicity, enhancement of endogenous immune responses and inhibition of angiogenesis. In 1995, Asaumi et al. [3] demon-

strated that CEP exhibits a direct antitumor effect in ICR mice exhibiting Ehrlich ascites tumor. This study showed that multiple administrations of the drug reduced tumor growth significantly compared to untreated tumors ($p < 0.001$).

A number of *in vivo* and *in vitro* studies have demonstrated the antitumor activity of CEP [9, 17, 21, 56, 79]. This antitumor action may be the result of the inhibition of Ca^{2+}-phospholipid-dependent protein kinase (PKC) mediated phosphorylation of cytoplasmic proteins, which causes a reduction in the interaction of these proteins with the plasma membrane [10].

Chemotherapy-potentiating effects

CEP has demonstrated potential as a chemotherapy-potentiating agent. In one study, CEP was shown to enhance the antitumor activity of vincristine and adriamycin in cultured L1210 cells [26]. In addition, the antitumor activity of methylglyoxal bis (cyclopentyl-amidinohydrazone), an inhibitor of polyamine biosynthesis, on human leukemic cells was potentiated by CEP [23].

Ono et al. tested the activity of chemotherapeutic agents, vincristine, vinblastine and vindesine with and without CEP against cancer cells both *in vitro* and *in vivo* [60]. In the *in vitro* study, the addition of CEP increased the antiproliferative activities of each vinca alkaloid between ten-fold and several hundred-fold. The *in vivo* study demonstrated that the administration of CEP at a dose of 5 mg/kg per day for 10 days with vincristine significantly enhanced the antitumor activity of vincristine in L1210 and P388 leukemia [26]. More recent data have shown that CEP at a concentration 10-fold lower than that used in some reported serum levels (0.3 μM) significantly increased vincristine-induced cell death in SMSR, SH-SY5Y and NB1691 neuroblastoma cell lines [8].

In addition, CEP augmented the ability of an immunotoxin to inhibit protein synthesis in KUT-1 and KUT-2 human T cell leukemia virus type-I infected T cell lines [54].

Multi-drug resistance

Multi-drug resistance (MDR) is a condition in which a tumor simultaneously becomes resistant to different classes of cytotoxic or cytostatic drugs and is commonly observed during cancer therapy. Several studies have demonstrated a significant benefit of CEP in reversing MDR, particularly for cancer agents such as doxorubicin, vincristine and paclitaxel [1, 11, 48]. CEP appears to restore the effect of anticancer drugs on MDR cells through a mechanism in which the plasma membrane function is disturbed, thereby leading to increases in the intracellular accumulation of these anticancer drugs [13, 15, 44, 66].

CEP has also been reported to synergistically accelerate doxorubicin-induced apoptosis in a p53-deficient human-resistant osteosarcoma [27]. Katsui et al. suggested that CEP may suppress the acidification of cytoplasmic organelles and consequently may be a useful modifier for anticancer drug therapies.

Induction and suppression of apoptosis

It is widely known that many anticancer drugs produce their therapeutic effect by inducing the apoptosis of malignant cells, which is mainly accomplished by activation of the cytochrome c/caspase-9 pathway [28]. Several studies have suggested that CEP also exerts apoptosis-inducing effects in some cancer cells [39, 70, 73, 77], thereby offering further potential for this drug as an anti-cancer agent [14].

It is interesting to note that CEP-induced apoptosis can be reduced or prevented by glutathione, which suggests that CEP does not act by affecting the integrity of the genome but initiates apoptosis through a direct effect on mitochondria [14, 46].

Allergies and inhibition of histamine release

The anti-allergic actions of CEP have been examined using experimental rat models of nasal allergy (rhinitis models) [35, 36]. In actively sensitized rhinitis models, CEP and ketotifen both inhibited the leak of dye into the perfusate of the nasal cavity in a dose-dependent manner. Kohno et al. suggested that these results demonstrate that CEP may be clinically effective for treating patients with nasal allergies and its anti-allergic mechanism may be the same as ketotifen's [35].

A study of CEP-treated mice reported in 1995 by Nakatsu et al. showed that CEP enhanced mitogen-induced histidine decarboxylase activity in the spleens of normal mice, genetically modified T cell-deficient nude mice and in T and B cell-deficient SCID mice [49].

In a canine model examining the excitatory responses of gastric movement and increases in gastric

mucosal histamine content caused by nerve stimulation or administration of tetragastrin, CEP inhibited the release of histamine from histamine-secreting cells in the gastric mucosa. This result suggests that histamine plays an important role in the neurohumoral excitatory mechanism of gastric movement and that CEP may affect this process [12].

Kondo et al. also demonstrated that CEP could inhibit histamine release from mast cells obtained from sensitized animals, which the authors claimed was due to the selective inhibition of T-cell-dependent immune reactions [38].

Experimental results suggest that the anti-allergic mechanism of CEP might be mediated by its membrane stabilizing action and by stimulation of pituitary-adrenotropic function [36]. A study investigating the mechanism underlying the inhibitory effect of CEP on phospholipase A2 activation in stimulated mast cells from rat peritoneum concluded that CEP suppressed receptor-mediated phospholipase A2 activation through, at least in part, uncoupling of GTP-binding proteins from the enzyme rather than by affecting the enzyme directly [2].

Inhibition of platelet aggregation

Several studies have demonstrated that CEP can aid in the inhibition of platelet aggregation. A number of experiments in rabbits have revealed that CEP inhibits platelet aggregation induced by collagen [22, 37, 62]. In an experiment in mice [63], a decrease in platelet number was diminished by the administration of 5 mg/kg CEP for six weeks, which suggested that CEP may prolong platelet lifespan.

Hashizume et al. suggested that CEP's inhibitory behavior on platelet aggregation was through an effect on the platelet signal transduction system at the point of the GTP-binding protein/phospholipase A2 complex [22].

Septic shock

CEP decreased the 24 h mortality rate in newborn rats undergoing endotoxic shock in a dose-related manner [16]. At the dose of 0.2 mg/kg, CEP effectively reduced the mortality from 90 to 21% in newborn rats. It also induced hyperglycemia in control rats and blunted the hypoglycemic response of endotoxic shock in treated rats.

Gram-negative bacterial components such as lipopolysaccharide (endotoxin) and cytokines have been implicated in the pathophysiology of endotoxic shock. TNF-α is a cytokine released from macrophages in response to endotoxins and has frequently been reported to cause symptoms similar to endotoxin shock. It has been reported that CEP protects mice against shock occurring through the endotoxin route and that attributed to the rhTNF-α/endotoxin-pathway [15, 45]. Although the mechanism by which CEP prevents rhTNF-α/endotoxin-induced shock is not yet clear, these findings suggest that CEP may have an effect against some of the pathologies mediated by pro-inflammatory cytokines during septic shock [15].

Nitric oxide (NO) has also been implicated in the pathogenesis of shock induced by endotoxin or TNF-α [73], which is dependent on several transcription factors, including NF-κB [41]. CEP was found to suppress TNF-α-induced stimulation of NF-κB activity [5], thereby suggesting that CEP may also decrease NO production by inhibiting NF-κB activation [57] and further help control septic shock.

Human immunodeficiency virus

A study of the inhibitory effects of CEP on TNF-α- and phorbol 12-myristate 13-acetate (PMA)-induced HIV-1 replication in chronically infected cell lines showed that CEP dose-dependently inhibited HIV-1 replication in TNF-α- and PMA-stimulated U1 cells [57]. CEP was found to suppress HIV-1 LTR-driven gene expression through the inhibition of NF-κB activation. These findings suggest that CEP is a highly potent inhibitor of HIV-1 replication in a chronically infected monocytic cell line.

In another study, the anti-viral effects of 96 derivatives of cepharanoline, including CEP, on HIV-1 replication in U1 cells were examined. Among the 12-O-alkyl derivatives, CEP proved to be the most active. The half maximal effective concentration of CEP in this study was 0.028 μg/ml (0.046 μM) [6].

The combination of CEP and K-12, a potent and selective inhibitor of HIV-1 transcription, was found to synergistically inhibit HIV-1 production in TNF-α-stimulated U1 cells, which are a promonocytic cell line chronically infected with the virus [58].

Malaria

In vitro growth inhibition studies have shown that CEP exhibits good antiplasmodial activity with the absence of a cytotoxic response [71]. At a dose of 10 mg/kg, CEP has been shown to cause a 47% decrease of ma-

larial parasitemia in mice through intraperitoneal injection and 50% decrease of parasitaemia by oral administration [7]. Similar results have been reported in an *in vivo* mouse model in which CEP inhibited parasite growth by 46% at a dose of 100 mg/kg of body weight [71]. Like chloroquine, CEP appears to inhibit the trophozoite stage of parasite growth.

Immunomodulatory effects

Experiments in mice have shown that CEP augments the natural killer (NK) activity of leukocytes isolated from the spleen, lymph node, lung and liver [59]. In addition, adherent leukocytes isolated from the lung or liver following CEP administration exhibit an augmented macrophage-mediated cytotoxicity. These results suggest that such organ-specific immune responses may play an important role in the antitumor and/or antimetastatic effects mediated by CEP [59].

Membrane-stabilizing effect and inhibition of plasma membrane lipid peroxidation

The anti-peroxidation activity and membrane stabilizing effect of CEP have been ascribed to its ability to scavenge radicals in solution such as hydroxyl radicals and 1,1-diphenyl-2-picrylhydrazyl (DPPH) as well as its ability to inhibit lipid peroxidation in mitochondria and liposomes by Fe^{2+}/ADP. As CEP is only effective at neutral pH values and not moderately acidic conditions, the authors concluded that the neutral form of the deprotonated amine moiety in the tetrahydroisoquinoline ring was responsible for the radical scavenging activity of CEP [33].

Antioxidant effects

There is strong evidence that CEP acts as an effective scavenger of free radicals, and it is this property that is believed to contribute to the many diverse effects exhibited by this biscoclaurine alkaloid [15].

In a comparative study of antioxidant activities, CEP showed a 94.6% inhibition of lipid peroxidation in a linoleic acid emulsion at a concentration of 30 μg/ml compared with 83.3% for butylated hydroxyanisole, 72.4% for α-tocopherol and 81.3% for trolox. These results demonstrate an effective antioxidant and radical scavenging activity for CEP [18].

DNA damage can be induced by constitutive ATM activation (CAA) and histone H2AX phosphorylation (CHP), which are processes that generate endogenous free radicals. In a study utilizing human lymphoblastoid TK6 cells, levels of CAA and CHP were lowered by up to 60% and 50%, respectively, following treatment with CEP [19]. Exposure to CEP also led to a decrease in the level of endogenous oxidants as measured by the ability to oxidate the fluorescent probe 5-(and 6)-carboxy-2',7'-dichlorodihydrofluorescein diacetate. The study researchers concluded that the scavenging properties of CEP may protect DNA from radicals generated endogenously during oxidative metabolism.

Clinical findings

The body of preclinical evidence suggesting a therapeutic benefit of CEP is compelling. However, controlled clinical data are clearly necessary to confirm these exploratory findings. The following sections summarize the clinical data available to date that demonstrate beneficial effects of CEP in a number of pathological conditions. These findings are also summarized in Table 1.

Radiation-induced leukopenia

Seven full clinical studies involving more than 350 patients have been conducted to examine the benefits of CEP for the control of leukopenia caused by radiation therapy for cancers of the head and neck [55], breast [68, 74], and lung [61, 69], as well as ovarian [76] and gynecological cancers [4]. The doses utilized in these studies were the following: 50 mg/kg in studies of ovarian and gynecological cancers [4, 76], 60 mg/day in both breast cancer studies [68, 74], 1 mg/kg per day for the lung cancer studies [61, 69], and 6 mg/kg per day for the study on head and neck cancers [55]. CEP was administered intravenously in the ovarian and gynecological cancer studies. All studies, without exception, demonstrated that CEP contributed to the prevention of leukopenia in patients who were treated with anticancer drugs. This important finding suggests that CEP may be able to reduce the period of risk for infection during radiation therapy, thereby allowing effective radiation regimens to be administered repeatedly over shorter intervals.

Tab. 1. Summary of case reports and clinical studies examining cepharanthine (CEP)

Property	Condition	Dose	Co-administration	Outcome	Ref.
Radiation-induced leukopenia	Head and neck cancer	6 mg/kg per day, *po*	None	CEP protected patients from leukopenia	[55]
	Breast cancer	60 mg/day, *po*	None	CEP reduced bone marrow suppression induced by adjuvant chemotherapy in primary breast cancer patients	[74]
	Breast cancer	60 mg/day, *po*	None	CEP reduced the rate of leukocytopenia	[67]
	Lung cancer	1 mg/kg per day, *po*	None	CEP was shown to have antileukopenic effect	[61]
	Lung cancer	1 mg/kg per day, *po*	None	CEP was shown to contribute to the prevention of leukopenia, especially neutropenia	[69]
	Ovarian cancer	50 mg/day, *po*	None	Administration of CEP during CDDP-ACR-CPA therapy was found to promote recovery from leukopenia and thrombocytopenia	[76]
	Gynecological malignant tumors	50 mg/day, *po*	None	CEP was found to contribute to the prevention of leukopenia	[4]
Leukocyte sequestration	Cardiopulmonary bypass	NS	None	CEP prevented the sequestration of leukocytes to the lung	[42]
Cancer management	Metastatic renal cell carcinomas	20 or 30 ml CEP solution (100 or 150 mg)	Vinblastine and adriamycin (intra-arterial injection)	Four of six patients exhibited a marked response to treatment, with a complete disappearance of the tumor vessel in two cases	[25]
	Prostate cancer	*po* or *iv*	None	Acute urinary toxicity was significantly milder for the intravenous group than for the oral group	[53]
	Renal cell carcinoma	10 mg, *iv*	None	CEP achieved partial response in 6 out of 12 cases and stable disease in 6 out of 12 cases	[75]
Idiopathic thrombocytopenic purpura	Steroid-unresponsive idiopathic thrombocytopenic purpura	40 mg/day, *po*	None	Continuous elevation of platelet counts was attained in 5 out of 22 patients 1 month after administration and 2 out of 22 patients 4 months after administration	[50]
	Idiopathic thrombocytopenic purpura in patients unable to discontinue steroid therapy	40-60 mg/day, *po*	None	Mean platelet counts increased significantly without side effects. In four out of nine patients, platelet counts were maintained at levels greater than $10 \times 10^4/\mu L$ 2 to 5 months after initiation of therapy	[32]
	Pediatric idiopathic thrombocytopenic purpura	1 mg/kg per day or 2 mg/kg per day	None	CEP restored platelet levels in both patients studied	[78]
Alopecia areata	Alopecia areata	NS	Topical squaric acid dibutylester (SADBE)	CEP plus topical SADBE achieved satisfactory hair regrowth in 6 out of 14 cases	[43]
	Common, atopic, pre-hypertensive or combined alopecia areata	1.5–6 mg	Kallikrein	CEP resolved common alopecia areata in 57% and 83% of patients within 3 and 6 months, respectively	[52]
Venomous snakebites	Patients of venomous snakebite by the Japanese viper	NS	Antivenin, methylpredni-solone	All 43 patients fully recovered activities of daily living, with neither organic disorders nor sequelae of the bitten extremities	[30]
Nodular muscular sarcoidosis	Nodular muscular sarcoidosis	4 mg/day, *po*	None	After 20 months, CEP completely resolved sarcoidosis in the one case reported	[51]
Multiple myeloma	Multiple myeloma	30 mg/day	Dexamethasone 10 mg/week	CEP achieved a marked reduction in M-protein count and normalization of platelet count, thereby indicating a considerable reduction in tumor load	[29]

Leukocyte sequestration during cardiopulmonary bypass

One clinical study reported in 1993 by Masuda et al. examined the effect of CEP on leukocyte sequestration to the lung during cardiopulmonary bypass without blood transfusion [42]. Six patients received methylprednisolone before and after the bypass, and five received CEP. Leukocyte sequestration to the lung was observed at the time of reperfusion only in those patients receiving methylprednisolone, thereby demonstrating that CEP prevented the sequestration of leukocytes to the lung. The authors suggested that this may be due to the membrane-stabilizing effect of CEP [42].

Cancer management

Several clinical trials examining the benefit of CEP on different aspects of cancer management have been performed. In 1994, Kakehi et al. examined the effect of multiple injections of 20 or 30 ml CEP solutions (100 or 150 mg CEP, respectively) over 1 or 30 min in combination with an intra-arterial injection of vinblastine and adriamycin (or epirubicin), which were administered to six metastatic renal cell carcinoma patients [25]. Four of these six patients exhibited a marked response to treatment, with a complete disappearance of the tumor vessel in two cases.

A retrospective analysis performed by Nomoto et al. analyzed the protective efficacy of CEP for toxicity to the bladder/urethra and rectum in 97 patients with prostate cancer who underwent radiotherapy [53]. These results suggested that intravenous CEP may prevent acute or late toxicity induced by radiotherapy for prostate cancer.

In a series of 12 cases of renal cell carcinoma, administration of 10 mg intra-arterial CEP for up to 10 cycles of therapy with a three to four week interval between cycles resulted in six cases showing a partial response and the other six showing stable disease progression. Resection of osseous metastases was performed in four cases. In two of these cases, no viable cancer cells were found. In the other two cases, only a small number of viable cancer cells were found.

Finally, CEP alleviated taste disorders and oral discomfort in 22 patients undergoing radiotherapy for head and neck cancer, thereby suggesting that CEP may be used to maintain quality of life in patients with this malignancy [64].

Idiopathic thrombocytopenic purpura (ITP)

Two clinical trials, both reported in 1992, have shown a benefit of CEP treatment in patients with idiopathic thrombocytopenic purpura (ITP). In the first study, reported by Kobayashi et al. [32], nine ITP patients who were unable to discontinue the administration of corticosteroids or immunosuppressive drugs were treated with high-dose oral CEP (40–60 mg/day), while the second study (Nakayama et al.) investigated 22 patients with steroid-unresponsive ITP treated with oral CEP at a daily dose of 40 mg [50]. In both studies, the mean platelet count increased significantly without any reported side effects. In the first study, elevated platelet counts persisted for up to five months [32].

Two case studies describing the use of CEP in pediatric recurrent ITP have been performed. In both cases, children with a low platelet count received platelet associated IgG at 42.7 ng per 107 platelets and γ-globulin, which restored platelet count to moderate levels. However, after administering CEP (1 mg/kg per day or 2 mg/kg per day), the platelet levels were fully restored [78].

Alopecia areata

Alopecia areata is a relatively benign condition that often resolves on its own. However, because its psychosocial impact on children and young adults can be severe, treatment is usually desirable.

In one case series [43], Morita et al. report that topical administration of the immunotherapy squaric acid dibutylester (SADBE) for a mean of 6.9 months in 14 patients with alopecia areata resulted in no or poor regrowth of hair in all cases. However, subsequent administration of a combination of topical SADBE treatment plus oral CEP for a mean duration of 7.6 months resulted in satisfactory regrowth of hair in six of the 14 cases [43].

In a series of case studies among 78 patients with differing types of alopecia areata (common, atopic or pre-hypertensive or combined), CEP doses between 1.5 and 6 mg were found to cure the condition within 2 months in 57% of patients and within 6 months in 86% of patients with common alopecia areata [52]. The combination of CEP (6 mg) with porcine pancreatic kallikrein (kallidinogenase) tablets was even more effective, resolving the condition in 90% of patients within three months of therapy.

Venomous snakebites

In a case series published in 1997 [30], Kimoto et al. reported that between 1990 and 1994, 43 consecutive patients bitten by the venomous Japanese viper *Agkistrodon halys* Blomhoffii were treated with a minimal dose of antivenin, methylprednisolone and CEP. All patients fully recovered and resumed their activities of daily living with neither organic disorders nor sequelae of the bitten extremities following this regime.

Nodular muscular sarcoidosis

In a case study involving a patient with nodular muscular sarcoidosis, oral administration of CEP at 4 mg/day for 3 months resulted in a reduction of serum ACE to normal levels [51]. After 10 months, the sarcoidosis had completely disappeared with no sign of relapse or reappearance 20 months after treatment (the time of publication).

Multiple myeloma

In a case study conducted by Kikukawa in Japan in 2008, a patient with multiple myeloma who was not responding to chemotherapy was given CEP to treat thrombocytopenia [29]. CEP was administered at a starting dose of 30 mg/day, and the dose then declined by 0.5 mg/day for 5 days. These researchers found that as the platelet count increased to 67,000/μl, the concentration of the M-protein decreased from 5.4 to 4.0 g/dl, which indicated a marked reduction in tumor load. After continuing with CEP at a dosage of 30 mg/day combined with once-weekly dexamethasone at 10 mg, M-protein was found to decrease below 3 g/dl and remained low for greater than 200 days, whilst the thrombocytopenia resolved. This single case study provides preliminary evidence to suggest that CEP may be useful in this notoriously difficult-to-treat malignancy.

Safety

Among clinical studies, CEP has not demonstrated any significant safety issues, and side effects were very rarely reported [25, 30, 42, 43, 50, 53, 55].

Conclusions

CEP is a fascinating pharmacological agent with a complex set of physiological actions and an array of clinical benefits. To date, preclinical and clinical studies have provided compelling evidence for the potential uses of CEP in preventing and treating radiation-induced leukopenia [4, 55, 61, 68, 69, 74], idiopathic thrombocytopenic purpura [32, 50], alopecia areata [43], alopecia pityrodes [Cepharanthine package insert, 2008], venomous snakebites and some aspects of cancer [25, 53, 72]. *In vitro* and *in vivo* studies have also suggested that CEP can act as an antitumor [3, 9, 10, 13, 20, 23, 26, 56, 60, 79] and anti-allergic agent [2, 12, 35, 36, 38, 49] and may have a role in the management of HIV [6, 57, 58] and malaria [7, 71]. It has also been reported to reverse multi-drug resistance [1, 11, 13, 27, 31, 44, 46, 48, 57, 67], potentiate chemotherapy [8, 26, 54], and display anti-inflammatory [16] and anti-oxidant effects [18].

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