Perillyl Alcohol: Applications in Oncology

by James T. Belanger, N.D.

Abstract

Perillyl alcohol is a monoterpene isolated from the essential oils of lavendin, peppermint, spearmint, cherries, celery seeds, and several other plants. In animal studies it has been shown to regress pancreatic, mammary, and liver tumors, to exhibit possible application as a chemopreventive agent for colon, skin, and lung cancer, and as a chemotherapeutic agent for neuroblastoma, and prostate and colon cancer. Perillyl alcohol is active in inducing apoptosis in tumor cells without affecting normal cells and can revert tumor cells back to a differentiated state. Its mechanism of action is unclear, but it has actions on various cellular substances which control cell growth and differentiation. It has been shown to increase mannose-6-phosphate/insulin-like growth factor II receptors, increase tissue growth factor beta receptors, increase Bak, decrease Ras protein prenylation, decrease ubiquinone synthesis, and induce Phase I and Phase II detoxification systems. Preliminary phase I human trials have not demonstrated consistent tumor regression at a three times daily dosage schedule. In addition, significant side-effects, mainly gastrointestinal, have been experienced with large doses.
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Introduction

Perillyl alcohol (POH), also called p-metha,1,7-diene-6-ol or 4-isopropenyl-cyclohexenecarbinol, is a monoterpene, and thus consists of two isoprene units manufactured by the mevalonate pathway.[1] It is found in small concentrations in the essential oils of lavendin, peppermint, spearmint, sage, cherries, cranberries, perilla *(Perilla frutescens)*, lemongrass, wild bergamot, gingergrass, savin, caraway, and celery seeds.[2]

Animal and *In Vitro* Studies

Many animal studies have shown perillyl alcohol to be a very powerful chemotherapeutic agent against several cancer types including pancreatic, breast, and liver cancer. Researchers at the University of Indiana measured the effects of varying concentrations of perillyl alcohol on human and hamster pancreatic tumor cell lines. Treatment of the pancreatic tumor cells for two days resulted in a dose-dependent decrease in cell proliferation, with IC50 values of 290 and 480 µM for the human and hamster cell lines, respectively. The control pancreatic tumor cells grew with a complete loss of contact inhibition, whereas the cell lines treated with perillyl alcohol grew in a monolayer.

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Based on these *in vitro* findings, Stark et al injected hamsters with pancreatic carcinoma cells and waited until tumors greater than or equal to 2 mm were palpated. At this point, the hamsters were given either a powdered diet mixed with 1.2-2.4 g/kg/day of perillyl alcohol (2-4% perillyl alcohol diet) or the powdered diet alone. After three weeks of chemotherapy, the average control tumor volume was 3121 +/- 120mm^3, whereas the average volume of perillyl alcohol-treated tumors was only 497 +/- 57mm^3 (p<0.05). Of the perillyl alcohol-treated pancreatic tumors, 5 of 25 completely regressed versus zero of 25 control tumors. There was no observable toxicity to the hamsters, and hematoxylin and eosin-stained sections of the liver, kidney, and normal pancreas showed no abnormalities.[3]
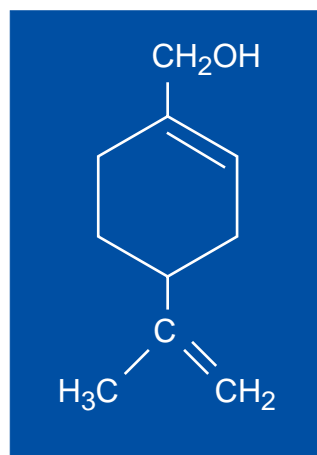
Stayrook et al found that thymidine incorporation into POH-treated malignant hamster pancreatic ductal epithelial cells and POH-treated nonmalignant hamster pancreatic ductal epithelial cells did not differ from that of controls. They concluded the inhibitory effects of POH on pancreatic cell growth was due to stimulation of apoptosis. The malignant cells treated with 100, 300, and 500 µM POH exhibited a 2.6, 8.8, and 18-fold higher rate of apoptosis, respectively, than the untreated malignant cells. The normal cells exhibited only a small increase in the percentage of cells that were apoptotic. POH appeared to cause cancer cells to undergo apoptosis by increasing the proapoptotic protein Bak. Bak expression was two-fold higher in POH-treated than untreated malignant hamster pancreatic ductal epithelial cells and Bak expression was unaffected in the non-malignant cells. Bak is known to be induced by wild type p53, a tumor suppressor gene, in response to DNA damage, but all of the pancreatic cancer cell lines tested in this experiment contained mutant p53, not wild-type, suggesting that the POH-induced increase in Bak expression is wild-type p53-independent.[4]

Gould and Haag at the University of Wisconsin conducted two separate studies in mice with mammary tumors induced by the carcinogen DMBA. In the first study, rats with tumors greater than or equal to 3 mm in diameter were randomly assigned to a control or a 2.5-percent (w/w) perillyl alcohol diet and were pair-fed. After three weeks of therapy, the 2.5-percent perillyl alcohol diet resulted in complete regression of the primary tumors in 22 of 27 (81%), whereas after nine weeks, the pair-fed controls had complete primary tumor regression in only 2 of 29 (31%). (Note: complete regression was defined as nonpalpability for a minimum of three consecutive weeks and partial regression was defined as regression to half or less of the original diameter).

In the second study, rats were randomly given either 0.0-, 0.5-, 1.0-, 1.5-, or a 2.0-percent perillyl alcohol diet for 15 weeks when the mammary tumors were greater than or equal to 10 mm in diameter, and allowed to feed ad libitum. Diets of 1-percent perillyl alcohol or higher showed a significant level of complete tumor regression. The 2-percent diet showed the greatest response with 10 of 20 having complete regression and 5 of 20 with partial regression. Histological sections at sites where perillyl alcohol induced complete tumor regression showed predominantly stromal tissue suggesting the monoterpene caused a redifferentiation of the tumor cells. Unlike the study by Stark et al,[3] a 3-percent perillyl alcohol diet caused several deaths. In this study, however,

Chemical structure of perylill alcohol.

a semipurified diet consisting of casein, corn starch, vitamins, minerals, choline, and methionine was used as the base instead of Purina powdered food.[5]

To study the effects of perillyl alcohol on liver tumors, Mills et al treated rats with the carcinogen diethylnitrosoamine (DEN) for one month. Two weeks after the removal of DEN, the animals were randomly placed on either Purina powdered food alone or powdered food containing POH at 1 percent (w/w) for the first week and 2 percent (w/w) thereafter. After 19 weeks of treatment the mean liver tumor mass was reduced by 10-fold in the POH group compared to the controls without any alteration in normal liver weight. Perillyl alcohol also caused a 5-fold increase in the apoptotic index in the large tumors (p<0.01) and a 10-fold increase in the apoptotic index in small tumors (p<0.001). The apoptotic index was very low (<0.1%) in the surrounding normal liver of untreated animals and was not altered by POH treatment. The perillyl alcohol-treated rats had an approximate 10-percent decrease in body weight compared to control rats, which was attributed to a decrease in body fat.[6]

In vitro studies indicated perillyl alcohol may also be active against neuroblastoma because it was found to induce differentiation in the neuroblastoma-derived cell line, Neuro-2A. Incubation of Neuro-2A cells with 1 mM perillyl alcohol also inhibited DNA synthesis within two hours, which continued over the 45 hours of the experiment and resulted in an almost complete inhibition of cellular proliferation.[7] Perillyl alcohol also inhibited the proliferation of prostate cancer cells *in vitro*.[8] Studies showed perillyl alcohol reversibly inhibited the proliferation response caused by lysophosphatidic acid in two human prostate cancer cell lines. Lysophosphatidic acid is generated by phospholipase D which is expressed by many prostate cancer cell lines and stimulates proliferation via a G1-independent pathway.[9]

Because of its effect on plasma IL-2 levels, it is speculated that perillyl alcohol may be a useful chemotherapeutic agent against adult T-cell leukemias, cutaneous T cell lymphoma, hairy cell leukemia, and Hodgkin's disease. These cancers are associated with elevated plasma IL-2 levels. T lymphoma cells, for instance, use IL-2 to promote their own proliferation by activating the MAP kinase cascade via phosphorylation. Activation of this cascade increases transcription factors which cause advancement of the cell cycle into the S or DNA replication phase. Concentrations of 100, 500, and 2500 µM perillic acid (PA), a perillyl alcohol metabolite, produced a dose-dependent inhibition of phytohemagglutinin-induced IL-2 generation to 80 percent, 60 percent, and 35 percent of control levels, respectively. Incubation of T lymphoma cells with 0, 1, 2, or 3 mM of PA even decreased the levels of phosphorylated MAP kinase after 48 hours incubation in a dose-dependent manner (60%, 45%, and 25% of controls). PA had this effect by depleting the geranylgeranylated small G-proteins, Rap1 and CDC42Hs, and the gamma 2 subunits of heterotrimeric G-proteins in a dose-dependent fashion. Triggering of the IL-2 receptor by IL-2 produced by the lymphoma and leukemia cells activates the G-proteins allowing them to bind GTP. The G protein-GTP complex activates the MAP kinase cascade which activates transcription factors such as activator protein 1 (AP-1) which increase DNA replication. Activation of AP-1 also synergizes with calcium/calcineurin-dependent signals for the induction of further IL-2 gene expression.[10]

Chemoprevention

As little as 2000 ppm of POH in the diet can inhibit AOM-induced adenoma and adenocarcinoma development in rat colons.[2] Transformation of colorectal epithelium to adenomas and carcinomas has been shown to be associated with a progressive inhibition of

apoptosis. Perillyl alcohol, as an agent which induces apoptosis, may prevent this transformation and thus be very useful in people with familial adenomatous polyposis, Gardner's syndrome, and hereditary nonpolyposis colorectal cancer.

Reddy et al fed a total of 108 rats either 1.0 g or 2.0 g of POH/kg or saline for two weeks before administering the carcinogen, azoxymethane (AOM). The carcinogen was given at two points, one week apart, while the rats remained on POH or the vehicle for a total of 55 weeks. The percent of control animals with invasive colon adenocarcinomas at week 55 was 27.7 percent versus 8.3 percent in the animals treated with 1 g/kg POH (p<0.05). The incidence and multiplicity of noninvasive colon adenocarcinomas was unaffected. The 2g/kg diet, for some unknown reason, only significantly inhibited the incidence of total colon adenocarcinomas. When invasive and non-invasive tumors were analyzed separately, the 2 g/kg diet had no significant effects. The 2 g POH/kg diet, however, significantly suppressed the incidence and multiplicity of small intestinal adenocarcinomas to 53 percent of the control (p<0.05). Both the 1- and 2 g/kg dose increased the apoptotic index by five to six-fold of the control (p<0.0001).[11]

In addition to preventing inhibition of apoptosis, perillyl alcohol may be protective against colon cancer and other cancers by enhancing the detoxification of carcinogens by the liver. Limonene, a monoterpene which yields the same metabolites as perillyl alcohol, has been shown to increase the urinary excretion of the carcinogen DMBA and its metabolites by 2.3-fold compared to control rats. When fed at a 5-percent diet two weeks before DMBA administration, limonene prevents DMBA from interacting with DNA by 50 percent when compared to controls. A 5-percent limonene diet can increase cytochrome P450 family members CYP2B and 2C, and increase epoxide hydratase, which are both members of the Phase I liver detoxification system, [12] and can induce Phase II detoxification systems.

When rats were fed a 5-percent limonene diet before the administration of the carcinogens CDNB (1-chloro-2,4-dinitrobenzene) and DCNB (3,4-dichloronitrobenzene), hepatic glutathione transferase (GST) more than doubled (p<0.05), the total amount of GST increased by 40 percent, and liver glutathione levels increased by about 28 percent (p<0.05). Limonene, however, had no effect on GST or glutathione levels, when the carcinogen EPNP (1,2-epoxy-3-[p-nitrophenoxy]propane) was given. The activity of both isoenzymes of uridine diphosphoglucuronosyl transferase (UDPGT: a Phase II enzyme important in conjugating the glucuronidation of planar aromatic hydrocarbons, aromatic amines, and their hydroxylated metabolites), also increased an average of 29 percent (p<0.05) on a 5-percent limonene diet when the substrates alpha-naphthol, chloramphenicol, and 4-OH-biphenyl were used.[13]

In addition to providing a protective role against colon cancer, perillyl alcohol may also inhibit the metastasis of already established colon tumors. D-limonene, which yields similar metabolites as perillyl alcohol, prevented murine colonic tumor cells implanted in the spleens of mice from seeding to the liver by 80 percent versus controls, at 35 days post-implantation.[14]

POH may also be helpful in reducing skin cancer occurrences. One week before the start of UV irradiation, mice were treated topically with 1- or 10 mM concentrations of (R)-(+)-POH or acetone three times a week. Five days per week for 18 weeks the mice were exposed to 30 minutes of UVB irradiation for a total dose of $1.1 \times 10^6 \, J/m^2/s$. Thirty minutes after irradiation three times per week, fifty microliters of either POH or acetone were

applied to each ear and 100 microliters were applied to the shaved dorsal surface. At 17 weeks of irradiation, control and 1 mM POH-treated mice had an average of approximately 0.4 nonmelanoma skin tumor per mouse and a tumor incidence of 37 percent, whereas 10 mM POH-treated mice had an average of only 0.1 tumor per mouse and a 7-percent incidence. Perillyl alcohol also reduced the erythema and dryness associated with the UV irradiation in a dose-dependent manner. The tumor incidence, however, started increasing in the 18th week and by the 20th week of the experiment, two weeks after the discontinuation of the UV irradiation and topical treatments, the tumor incidence increased in the POH-treated mice to almost the level of the control mice, suggesting that perillyl alcohol delayed the formation of the skin tumors. At 22 weeks, mice treated with 10 mM POH had an average of 32 mm^2 tumor area as compared to 100 mm^2 in acetone controls.

Topical application of perillyl alcohol did not cause any change in body weight or behavior in irradiated mice, suggesting no systemic toxicity. As determined by punch biopsies, topical application of 100 mM POH inhibited UV-induced transactivation of activator protein 1 (AP-1) by 75 percent. AP-1 is induced by UVB and UVC through a phosphorylation cascade transduced from Ras. Inhibition of Ras blocks UVC-induced AP-1 transactivation. Ras, atypical protein kinase C, mitogen-activated protein kinase, Raf and Jun amino-terminal kinase have been shown to play a role in UVB and UVC signal transduction. It is possible that perillyl alcohol blocks one of these signal transducers and in doing so inhibits the transactivation of AP-1.[15] Perillyl alcohol may even be active against melanoma. Murine B16 melanoma cells were incubated with perillyl alcohol for 48 hours. A concentration of 250 +/- 28 µmol/L suppressed the increase in the population of melanoma cells by 50 percent.[16]

POH may prevent tobacco-induced lung cancer. In a study by Lantry et al, mice were randomized into groups. Group 1 received 75 mg/kg POH intraperitoneally (ip) three times per week and 100 mg/kg of NNK ip; group 2 received only POH; group 3 received NNK alone; and group 4 received vehicle. NNK, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone, is a suspected etiologic agent in tobacco-related human cancer. NNK is metabolized by cytochrome P450 enzymes into compounds which can alkylate K-ras gene DNA resulting in oncogenic transformation. Human lung cancer frequently has activated K-ras mutations. POH treatment was started one week before the introduction of the carcinogen and was continued for 22 weeks. The carcinogen was given twice during the experiment. The incidence of adenoma tumors in group 3 (NNK only) was 100 percent, whereas POH reduced the tumor incidence to 78.6 percent and tumor multiplicity to 1.86 +/- 1.66 tumors per mouse (58%).[17]

Mechanisms

The exact mechanism of perillyl alcohol tumor regression is unknown but it appears to alter several cell parameters which include increasing mannose 6-phosphate/insulin-like growth factor II receptors; increasing transforming growth factor beta type I, II, and III receptors; decreasing p21ras protein synthesis and increasing p21ras catabolism; decreasing nuclear lamin B in actively replicating cells; and inducing Phase I and Phase II liver detoxification systems.

In order to determine how POH works *in vivo*, rats with mammary tumors were randomly assigned either a plain base diet or a base diet with 2-percent POH. After two weeks on the diet, 10 µl of [^{14}C]mevalonolactone was infused into their mammary glands and three hours later the glands were removed and the mammary epithelial cells were analyzed for protein prenylation, coenzyme Q synthesis,

and cholesterol synthesis. In the control rats ^{14}C-labeled small G proteins, coenzyme Q, and cholesterol were detectable at three hours post-infusion. Rats given the 2-percent POH diet had a 20 percent inhibition of small G protein isoprenylation and CoQ synthesis. Cholesterol synthesis was unaffected. Of the G proteins, Ras prenylation by farnesyl protein transferase (FPTase) was inhibited by 17 percent and RhoA prenylation by type I geranylgeranyl protein transferase (GGPTase) was inhibited by 28 percent.

In an NMU-induced rat mammary tumor preventive study, dietary monoterpenes reduced the average number of tumors per rat by 50 percent but did not alter the percentage of tumors with activated Ras. This suggests the modest inhibition of Ras farnesylation by POH does not underlie the prevention of mammary cancer by monoterpenes. It has not been ruled out, however, if the POH-induced inhibition of RhoA prenylation by type I GGPTase inhibits mammary tumor growth. Rac1 and RhoA, two substrates for type I GGPTase, have transforming potential in cultured cells and play important roles in cell signaling and cytoskeleton organization. Inhibiting their post-translational prenylation prevents them from entering the plasma membrane and, in turn, inactivates them.[18]

Reducing coenzyme Q synthesis could also inhibit tumor growth by decreasing ATP synthesis in the electron transport chain. Because coenzyme Q is a powerful antioxidant, inhibition of its synthesis may make tumor cells more vulnerable to free radical damage.[19] Coenyzme Q located in plasma membranes is also important in transducing signals for cellular proliferation. Activated Ras oncogenes in tumor cells cause generation of a significant amount of endogenous hydrogen peroxide, compared to normal cells which can oxidize coenzyme Q in the plasma membranes. When plasma membrane coenzyme Q is in the oxidized state, tyrosine kinases are activated.

Tyrosine kinases play a role in signaling nuclear factors such as c-myc and c-jun to increase transcription to cause cellular proliferation.[20] Arguing against this mechanism of inhibiting tumor growth are the case reports of coenzyme Q10 regressing metastatic breast cancer.[21,22] Shi and Gould also showed that supplementing perillyl alcohol-treated Neuro-2A neuroblastoma cells with CoQ9 supplementation had no effect in preventing POH-induced neurite differentiation.[8]

Mills et al found that a 2-percent perillyl alcohol diet for 19 weeks in rats with DEN-induced liver tumors increased the mRNA levels for TGF-beta type I, II, and III receptors in large tumors by 100 percent (p=0.025), 38 percent (p=0.05), and 49 percent (p=0.04), respectively, compared to the mRNA levels in large tumors from untreated animals. POH caused no effect on TGF-beta mRNA levels in normal livers. Perillyl alcohol also increased the mean level of mannose-6-phosphate/insulin growth factor II receptor mRNA by more than 100 percent in large liver tumors compared to the normal surrounding tissue. Untreated liver tumor tissue had an M6P/IGFII receptor mRNA increase of 50 percent compared to its surrounding tissue. M6P/IGFII receptors function in part to bind the TGF-beta/TGF-beta-binding protein complex and IGFII.[7] IGFII can have a mitogenic effect on mammary tumors by binding to IGF-I receptors. The increased levels of the M6P/IGFII receptor induced by perillyl alcohol may interfere with mammary tumor growth by internalizing and degrading the mammary associated growth factor, IGF-II.[23] Tumor cells such as human breast cancer cells synthesize and secrete a latent form of TGF-beta which requires the mannose 6-phosphate receptor and plasmin to activate it; thus, POH indirectly activates TGF-beta by increasing M6P receptors. Activated TGF-beta induces G1 cell cycle blockage and DNA synthesis arrest in low concentrations (0.5 ng/ml), and apoptosis in higher concentrations (2.5 ng/ml).[24]

It has been shown that a loss of sensitivity to growth inhibition by endogenous TGF-beta may contribute to the process of tumorigenesis in colon cancer. Some studies, however, show that TGF-beta overexpression may enhance tumorigenesis and when antibodies to TGF-beta 1,2 and 3 are injected into mice with mammary carcinomas, lung metastasis is prevented. There is a possibility that TGF-beta may play a protective role early in breast cancer tumorigenesis and a detrimentally enhancing role later in breast cancer tumorigenesis; thus, perillyl alcohol in later stages in breast cancer may be harmful. This has yet to be confirmed in human trials. Jirtle et al speculated that tumors unresponsive to POH may contain a modification in the expressed M6P/IGF-II receptor gene which prevents POH from upregulating it.[23]

Perillyl alcohol also caused a decrease in G1 cyclin D1 protein levels by 50-70 percent in mammary cancer cells after a 5-hour incubation. Cyclin D1 allowed cancer cells to enter the S or DNA replication phase more readily, and thus, perillyl alcohol caused a G1 block.[25]

Pharmacokinetics

The most accurate method of measuring perillyl alcohol and its metabolites perillic acid and dihydroperillic acid is by isocratic high-performance liquid chromatography.[26,27] Studies in humans and dogs demonstrated perillyl alcohol was rapidly absorbed within minutes when given orally, and quickly metabolized into perillic acid and dihydroperillic acid. In humans peak plasma levels of perillic acid (PA) occur approximately 1.5-3.5 hours after ingestion and 3-5 hours after ingestion for dihydroperillic acid (DHPA). Concentrations of PA are about fourteen times that of DHPA. The half-life for each metabolite is approximately two hours.

Metabolite peak levels and 6-hour AUCs (area under the concentration time curve) for PA initially increased as the dose of perillyl alcohol increased, but after 29 days of treatment they were not statistically different. For example, by day 29 the average peak plasma concentration of PA after a dose of 800 mg/m^2 and 1600 mg/m^2 of perillyl alcohol was 139 +/- 88 µ M and 311 +/- 152 µM, respectively. The peak plasma concentrations of DHPA, however, statistically increased from 9.8 +/- 5.6 µM to 34.0 +/- 23.0 µM at day 29 after increasing perillyl alcohol's dose from 800 mg/m^2 to 1600 mg/m^2. Increasing doses further to 2400 mg/m^2 actually decreased the plasma levels of PA and DHPA when compared to 1600 mg/m^2. It was speculated this could have been due to a saturation of a carrier-mediated transport system or an interference from the soybean oil which was combined with the perillyl alcohol. Also, it is possible liver detoxification enzyme systems were upregulated.[18]

Perillyl alcohol is also probably absorbed into the skin very efficiently. In a study by Williams and Barry various terpenes were assessed for skin penetration abilities. Perillyl alcohol was not tested, but various similar terpene alcohols were effective in disrupting the lipid structure of the stratum corneum and were useful agents for carrying more polar drugs through the skin.[28]

Results from rat studies showed that tumor regression occurred when plasma levels of the perillyl alcohol metabolites PA and DHPA, reached 390-480 µM and 110-230 µM, respectively. Pharmacokinetic studies in humans show PA plasma levels between 390-480 µM can be achieved in some patients when nontoxic doses of perillyl alcohol are given orally. Plasma levels of DHPA, however, only reached about 34 +/- 23.0 µM in humans. It is uncertain if a higher plasma level of DHPA is needed to achieve tumor regression in humans.

Phase I Human Trials

To date, three phase I trials of perillyl alcohol have been conducted. Doses were as high as 2.8 g/m^2 TID orally, and only a few patients showed evidence of antitumor activity. One ovarian cancer patient experienced a decline in CA125, and several other patients experienced stabilization of their disease for up to six months. It has been speculated a TID dosing schedule may not be as effective as a more frequent dosing schedule because of the short half-life of the metabolites.[18]

The animals in various studies which had tumor regression were given food mixed with about 2-percent POH and were allowed to feed ad libitum. A 2-percent diet provides approximately 1.76 g POH/kg/day which is equivalent to 20 g/day for a 70-kg human adult.[5] Giving the nontoxic dose of 1.6 g/m^2 of perillyl alcohol five times a day to simulate ad libitum provides about 20 g/day and may then yield results in humans similar to the animal studies. Currently a phase II trial is being conducted in patients with ovarian cancer using a QID dosing schedule to test this hypothesis.

Toxicity

Histopathological studies of rats and dogs given 900-1200 mg/kg/day of perillyl alcohol orally in 2-3 divided doses revealed forestomach epithelial hyperplasia, necrosis and/or erosion; and renal tubular and testicular degeneration. Blood urea nitrogen and ALT levels increased, and renal and thymus lesions were apparent by the 28th day of the study. The 1000 mg/kg/day dose also caused splenic atrophy and hepatocyte cytoplasmic vacuolization. All of the effects were reversible except testicular atrophy. Lower doses of 400 mg/kg/day caused no signs of toxicity in rats, but produced emesis and a mild anemia in dogs.[29]

The results of three trials in humans indicated the most common toxicity from orally dosed POH was gastrointestinal (GI).

In one phase I trial, a total of eighteen patients with various tumor types including prostate, ovarian, and breast cancer, were started on escalating doses of perillyl alcohol beginning at 0.8 g/m^2 TID. Four, seven, and seven patients completed three months of oral POH therapy at the respective doses of 0.8, 1.6, and 2.4g/m^2 TID. Two patients at the highest dose experienced grade 3 nausea and vomiting, and two patients experienced grade 2 nausea and vomiting. One patient at the highest dose experienced grade 2 diarrhea. Patients at the highest dose also frequently complained of anorexia, satiety, eructation, and unpleasant taste. The medium and low dose, however, caused much milder GI symptoms. In fact, only one patient experienced grade 2 nausea and vomiting. Two of the phase I trials indicated the patients received perillyl alcohol on an empty stomach. In the other phase I trial that information was not provided. In the animal studies, however, perillyl alcohol was given with food, and animals did not exhibit GI symptoms at therapeutic doses and absorption was not impaired.

In addition to GI symptoms, patients at all three dosage levels complained of fatigue, but it was generally mild (grade 1-2). No evidence of hepatic, renal, or neurological toxicity was observed. Two ovarian cancer patients who had received prior chemotherapy experienced grade 3 neutropenia during their second and third months of therapy. One patient was receiving the high dose of POH and one the medium dose. In both patients, the toxicity resolved within 1-2 weeks after stopping the drug.[18]

Another phase I trial done at Yale University dosed cancer patients at 1.6 g/m^2, 2.1 g/m^2, or 2.8 g/m^2 TID orally for eight weeks. Patients at the low dose had no signs of toxicity; however, the patients at the medium dose experienced loss of appetite, fatigue, weight loss, nausea, and vomiting on a daily basis. Patients at the highest dose

experienced severe fatigue, slurred speech, short term memory loss, and stumbling.[30] Results at the Fox Chase Cancer Center using the same dosing schedule as the Yale University trial showed similar results, but patients at 2.1 and 2.8 g/m^2 also experienced grade 1-2 hypokalemia.[31]

Conclusions

In animals, perillyl alcohol is an effective chemotherapeutic agent for pancreatic, breast, and liver cancer, and a chemopreventive agent for skin, lung, and intestinal cancer. Phase I trials have failed to show a substantial therapeutic effect in humans, but phase II trials are presently being conducted for further evaluation. Future phase II trials will take into account the short half-life of the perillyl alcohol metabolites and will dose the drug more frequently at 1.6 g/m^2/dose. In this way, the dosing schedule will be more similar to animal studies and hopefully better results will be achieved.

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