Perillyl alcohol

Perillyl alcohol (POH) is a naturally occurring dietary monoterpene isolated from the essential oils of lavender, peppermint, and other plants. Medical interest in this compound was generated by research findings showing that POH was able to inhibit the growth of tumor cells in cell culture and exert cancer preventive and therapeutic activity in a variety of animal tumor models. Based on this promising preclinical work, POH was formulated in soft gelatine capsules and orally administered to cancer patients several times a day on a continuous basis. However, such clinical trials in humans yielded disappointing results, also because the large number of capsules that had to be swallowed caused hard-to-tolerate intestinal side effects, causing many patients to withdraw from treatment due to unrelenting nausea, fatigue, and vomiting. As a result, efforts to treat cancer patients with oral POH were abandoned and did not enter clinical practice. Intriguingly, clinical trials in Brazil have explored intranasal POH delivery as an alternative to circumvent the toxic limitations of oral administration. In these trials, patients with recurrent malignant gliomas were given comparatively small doses of POH via simple inhalation through the nose. Results from these studies show this type of long-term, daily chemotherapy to be well tolerated and effective [1)].

Intracarotid injection of mannitol has been applied for decades to support brain entry of therapeutics that otherwise do not effectively cross the blood-brain barrier (BBB). However, the elaborate and high-risk nature of this procedure has kept its use restricted to well-equipped medical centers. Wang et al. are developing a more straightforward approach to safely open the BBB, based on the intraarterial (IA) injection of NEO100, a highly purified version of the natural monoterpene perillyl alcohol.

In vitro barrier permeability with NEO100 was evaluated by transepithelial/transendothelial electrical resistance (TEER) and antibody diffusion assays. Its mechanism of action was studied by western blot, microarray analysis, and electron microscopy. In mouse models, we performed ultrasound-guided intracardiac administration of NEO100, followed by intravenous application of Evan's blue, methotrexate, checkpoint-inhibitory antibodies, or chimeric antigen receptor (CAR-T) cells.

NEO100 opened the BBB in a reversible and non-toxic fashion in vitro and in vivo. It enabled greatly increased brain entry of all tested therapeutics and was well tolerated by animals. Mechanistic studies revealed effects of NEO100 on different BBB transport pathways, along with translocation of tight junction proteins from the membrane to the cytoplasm in brain endothelial cells.

They envisioned that this procedure can be translated to patients in the form of transfemoral arterial catheterization and cannulation to the cerebral arteries, which represents a low-risk procedure commonly used in a variety of clinical settings. Combined with NEO100, it is expected to provide a safe, widely available approach to enhance brain entry of any therapeutic [2)].

Silva-Hirschberg et al. investigated the potential anticancer effects of NEO212, a novel compound generated by covalently conjugating perillyl alcohol (a natural monoterpene) to temozolomide (an alkylating agent), on MF and SS cell lines in vitro. HUT-78, HUT-102, and MyLa cells were treated with NEO212 under different conditions, and drug effects on proliferation, viability, and apoptosis were characterized.

Results: NEO212 inhibited proliferation, diminished viability, and stimulated apoptosis in all cell lines,

although with varying degrees of potency in the different cell lines. It down-regulated c-myc and cyclin D1 proteins, which are required for cell proliferation, but triggered endoplasmic reticulum stress and activation of caspases. Pretreatment of cells with antioxidants ascorbic acid and beta-mercaptoethanol prevented these NEO212-induced effects.

Conclusions: NEO212 exerted promising anticancer effects on SS and MF cell lines. The generation of reactive oxygen species (ROS) appears to play a key role in the NEO212-induced cell death process, because the blockage of ROS with antioxidants prevented caspase activation. We propose that NEO212 should be investigated further toward clinical testing in these tumor types [3)].

Chen et al. synthesized a TMZ analog where the natural product perillyl alcohol (POH) was covalently linked to TMZ's amide functionality. The resulting novel compound, called TMZ-POH (T-P), displayed greatly increased anticancer activity in a variety of breast cancer cell lines, inclusive of TMZ-resistant ones. It caused DNA damage and cell death much more efficiently than its parental compound TMZ, because linkage with POH increased its biologic half-life and thus provided greater opportunity for placement of cytotoxic DNA lesions. In an intracranial mouse tumor model with triple-negative breast cancer, T-P revealed considerably greater therapeutic efficacy than TMZ, where a single cycle of treatment extended median survival benefit from 6 days (in the case of TMZ) to 28 days. At the same time, T-P seemed to be well tolerated by the animals. Thus, T-P may have potential as a novel therapy for brain-targeted breast cancer metastases [4)].

Cho et al. explored the effects of the novel agent NEO212, a conjugate of temozolomide to perillyl alcohol, on temozolomide-resistant gliomas. NEO212 was tested for cytotoxic activity on three human temozolomide-resistant glioma cell lines, which were resistant to temozolomide based on overexpression of the base excision repair (BER) pathway, mismatch repair (MMR) deficiency, or overexpression of O(6) methyl-guanine-DNA methyltransferase (MGMT). BER expression was evaluated by Western blotting and PARP activity. MMR deficiency was determined by Western blotting and microsatellite instability. MGMT overexpression was evaluated by Western blotting and O(6)-benzylguanine (O(6)BG) inhibition. For in vivo evaluation of NEO212, temozolomide-resistant glioma cells were implanted into immune-incompetent mice, and NEO212 was administered. NEO212, at equimolar concentrations of temozolomide, was more cytotoxic for temozolomide-resistant cells than temozolomide and not toxic to normal cells. NEO212-induced cell death in temozolomide-resistant glioma cells was independent of such mechanisms of resistance as high levels of MGMT, MMR deficiencies, or overexpression of BER proteins. NEO212 functions as a DNA alkylating agent, similar to temozolomide; however, this novel conjugate is unique for it may induce endoplasmic reticulum (ER) stress and inhibits autophagy. In vivo studies show that NEO212 reduces intracranial tumor growth and increases animal survival without significant toxicity. These results demonstrate that NEO212 is an effective drug against malignant gliomas that can be used for a broad range of newly diagnosed and temozolomide-resistant gliomas [5)].

Perillyl alcohol (POH) is a monoterpene that has been used orally for the treatment of systemic cancer. However, when used orally significant gastrointestinal side effects and lack of overall efficacy were documented. Recently, in a phase II trial in Brazil for the treatment of temozolomide (TMZ)-resistant malignant gliomas, POH was well tolerated when administered intranasally. The present study explores the effects and mechanisms of POH on TMZ-sensitive and TMZ-resistant glioma cells.

In vitro studies showed that POH was cytotoxic to TMZ-resistant as well as TMZ-sensitive glioma cells, and this effect was independent of O(6)-methylguanine-DNA methyltransferase expression. POH induced cytotoxicity, in part, through the endoplasmic reticulum (ER) stress pathway as shown by the increased expression of glucose-regulated protein-78 (GRP78), activating transcription factor 3, and C/EBP-homologous protein. In addition, POH impeded survival pathways, such as mTOR and Ras. As well, POH reduced the invasive capacity of sensitive and resistant glioma cells. POH alone and/or in combination with other ER stress-inducing cytotoxic drugs (i.e., 2, 5-dimethyl-celecoxib, nelfinavir) further induced apoptosis in TMZ-sensitive and TMZ-resistant glioma cells. To show whether intranasal delivery of POH was effective for the treatment of TMZ-resistant gliomas, animals bearing intracranial tumors were given POH intranasally. Animals treated through intranasal administration of POH exhibited a decrease in tumor growth and an increase in survival. Our data show that POH is an effective anti-glioma cytotoxic agent for TMZ-resistant gliomas when administered intranasally [6].

References

1)

Chen TC, Fonseca CO, Schönthal AH. Preclinical development and clinical use of perillyl alcohol for chemoprevention and cancer therapy. Am J Cancer Res. 2015;5(5):1580-1593. Published 2015 Apr 15.

2)

Wang W, Marín-Ramos NI, He H, et al. NEO100 enables brain delivery of blood-brain barrier-impermeable therapeutics [published online ahead of print, 2020 Sep 2]. Neuro Oncol. 2020;noaa206. doi:10.1093/neuonc/noaa206

3)

Silva-Hirschberg C, Hartman H, Stack S, et al. Cytotoxic impact of a perillyl alcohol-temozolomide conjugate, NEO212, on cutaneous T-cell lymphoma in vitro. Ther Adv Med Oncol. 2019;11:1758835919891567. Published 2019 Dec 6. doi:10.1177/1758835919891567

4)

Chen TC, Cho HY, Wang W, et al. A novel temozolomide-perillyl alcohol conjugate exhibits superior activity against breast cancer cells in vitro and intracranial triple-negative tumor growth in vivo. Mol Cancer Ther. 2014;13(5):1181-1193. doi:10.1158/1535-7163.MCT-13-0882

5)

Cho HY, Wang W, Jhaveri N, et al. NEO212, temozolomide conjugated to perillyl alcohol, is a novel drug for effective treatment of a broad range of temozolomide-resistant gliomas. Mol Cancer Ther. 2014;13(8):2004-2017. doi:10.1158/1535-7163.MCT-13-0964

6)

Cho HY, Wang W, Jhaveri N, et al. Perillyl alcohol for the treatment of temozolomide-resistant gliomas. Mol Cancer Ther. 2012;11(11):2462-2472. doi:10.1158/1535-7163.MCT-12-0321