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Patient with recurrent grade 4 astrocytoma responding favorably to intranasal delivery of NEO100, highly pure perillyl alcohol: illustrative case

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BACKGROUND Better treatments are needed for patients with grade 4 gliomas, especially in the setting of recurrence. The authors are developing NEO100, a clinical-grade version of the natural monoterpene perillyl alcohol, as a cancer therapeutic to be administered via intranasal (IN) delivery to patients with recurrent glioma.

OBSERVATIONS A 40-year-old woman was diagnosed with an isocitrate dehydrogenase 1–mutant, CNS WHO grade 4 astrocytoma harboring an unmethylated MGMT promoter. She underwent surgery and standard chemoradiation treatment with temozolomide (TMZ), but after 6 cycles of adjuvant TMZ, the tumor recurred. The patient was started on daily IN NEO100 at 288 mg 4 times a day, administered using a nebulizer and nasal mask. Routine MRI revealed steady tumor regression over the course of 13 months of daily IN NEO100, to the point where the tumor became inconspicuous. There were no serious adverse events, and her quality of life improved and remained high.

LESSONS The authors present a case in which IN cancer therapy with NEO100 was well tolerated and was associated with striking tumor regression, providing further evidence that this novel conceptual approach to cancer therapy might become useful for the improved treatment of recurrent glioma.

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KEYWORDS O^6-methylguanine-DNA methyltransferase; case report; chemoresistance; intranasal drug delivery; isocitrate dehydrogenase; recurrent glioma

The most recent WHO classification of tumors of the CNS[1] utilizes characteristic mutations in isocitrate dehydrogenase genes (*IDH1* and *IDH2*) to differentiate between astrocytoma, IDH mutant, and glioblastoma (GBM), 2 primary glial neoplasms that can have histological overlap. Combined, these tumor types represent the most common and deadliest malignant brain tumors among adults. Regardless of the treatment regimen, the disease relapses in the vast majority of these patients, who are left with limited treatment options. The disease does not respond well to repeat surgery, re-irradiation, or additional rounds of chemotherapy or immunotherapy; therefore, the prognosis of these patients continues to remain exceptionally poor.

In view of the persistent medical need for improved treatments, we are investigating a novel type of intervention: intranasal (IN) delivery of NEO100, a highly pure, pharmaceutical-grade version of perillyl alcohol (POH), also called "*p*-mentha,1,7-diene-6-ol." POH is a naturally occurring monoterpene related to limonene that is present in the essential oils of lavender, citrus fruit peel, peppermint, and several other plants, where it is synthesized through the mevalonate pathway.[2] A number of preclinical studies have provided solid evidence of its in vitro and in vivo anticancer potency in a variety of tumor models.[3,4] Early on, studies showed that POH inhibited the enzymatic activity of farnesyl-protein transferase in the mevalonate pathway, which caused

ABBREVIATIONS FISH = fluorescence in situ hybridization; GBM = glioblastoma; IN = intranasal; mOS = median overall survival; PA = perillic acid; POH = perillyl alcohol; RTT = Right to Try; TMZ = temozolomide.

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inhibition of the oncogenic activity of Ras protein, as the latter requires posttranslational farnesylation for plasma membrane anchoring and mitogenic activity.[5] Additional cellular effects of POH were discovered, such as inhibition of the cytoplasmic sodium/potassium transporter, which triggers proapoptotic endoplasmic reticulum stress due to the ensuing electrolyte imbalances, and inhibition of telomerase, which causes senescence and prevents further cell proliferation. Combined, these pleiotropic effects of POH result in cell cycle arrest in the G1 phase and inhibition of tumor cell growth, eventually leading to apoptosis (see detailed citations in the review by Chen et al.[6]).

Despite the consistently observed anticancer activity in a variety of preclinical models, numerous phase 1 and 2 trials in patients with different solid tumors were unable to demonstrate convincing therapeutic activity in the clinic (see detailed references in the review by Chen et al.[6]). In these studies, POH was formulated in gelatin capsules and given orally in relatively large doses of several grams, 3–4 times daily, for several months. Gastrointestinal toxicity proved limiting, and some patients were forced to quit the trials due to unrelenting, chronic malaise (fatigue, nausea, belching, reflux, diarrhea, or constipation).[7–9] In addition, therapeutic activity was unconvincing. As a result, oral POH was abandoned and did not enter clinical practice. In retrospect, the failure of oral POH, at least in part, was due to its extensive metabolism by the liver. Efficient POH breakdown by liver enzymes is well characterized,[10] and only POH metabolites, but not intact POH, could be detected in the plasma of treated patients.[11,12]

Nasal delivery of chemotherapy is envisioned as a novel, paradigm-shifting platform to deliver therapeutics to the brain while minimizing systemic toxicity and first-pass metabolism.[13–15] Effective nose-to-brain delivery has been demonstrated in a variety of noncancer conditions, such as migraine, stroke, and other neurological conditions.[16–18] For example, IN insulin has been shown to improve cognition in early Alzheimer's disease.[19,20] Although not yet fully characterized, the presumed mechanism of brain drug uptake after IN delivery is thought to involve the olfactory and trigeminal nerves and the nasal mucosa. Combined, these elements facilitate direct access and quick absorption of drugs, thereby resulting in greater bioavailability, rapid onset of drug responses, and protection from breakdown in the liver.[21,22] However, despite these distinct benefits, IN delivery of cancer therapeutics is not established in clinical practice.

To investigate the potential benefits of IN drug delivery for brain cancer therapy, we developed NEO100, a highly pure version of POH produced under current good manufacturing practice conditions. A phase 1 clinical trial,[23] conducted in 12 adult patients with recurrent GBM (diagnosed before the establishment of the new WHO classification of CNS tumors), investigated the safety of IN NEO100 at escalating dosages and demonstrated the remarkable safety of this approach. When looking for preliminary signs of activity, it was noted that the median overall survival (mOS) was 15 months, which represented a highly encouraging outcome in view of a generally expected average survival of 6–10 months for this patient group.[24–27] When patients were stratified according to their IDH status, it was noted that patients with IDH1-mutant status (n = 5) fared even better on average (4 patients alive at 24 months) than those with an IDH-wildtype status (n = 7; no survivors at 24 months).[23] For this reason, the inclusion criteria of the ongoing phase 2a trial were expanded to include patients with grade 3 IDH-mutant astrocytoma.

While phase 2a of IN NEO100 continues, patients can also be considered under the United States Right to Try (RTT) pathway, which represents a pathway for patients diagnosed with life-threatening diseases, who have exhausted all approved treatment options to receive unapproved medical care. Here, we report on such a patient, a female with recurrent astrocytoma, IDH1 mutant, CNS WHO grade 4, MGMT promoter unmethylated, who has been under daily IN NEO100 treatment for 13 months and has shown remarkable tumor regression without severe side effects. Her treatment was the same as that applied in an ongoing clinical trial, an open-label, phase 1/2a dose escalation safety and efficacy study of NEO100 in recurrent or progressive grade III or grade IV IDH1 mutated glioma (ClinicalTrials.gov identifier no. NCT02704858). However, because her recurrent glioma was larger than 3×3 cm^2, she was not considered a candidate for this trial and instead received treatment under the RTT Act. Both the ongoing phase 1/2a clinical trial and the RTT pathway are sponsored by NeOnc Technologies, Inc.

Illustrative Case

A woman with recurrent grade 4 astrocytoma has been undergoing treatment with IN NEO100 for well over a year. At age 40 years, in November 2021, the patient presented with symptoms of visual aura with flashing lights, headache, nausea, vomiting, and generalized tonic-clonic seizure. A partially necrotic left parietal lobe mass was identified and resected in February 2022. Neuropathological examination (Fig. 1) revealed an infiltrative glial neoplasm with microvascular proliferation and elevated mitotic activity. Fluorescence in situ hybridization (FISH) was negative for 1p/19q codeletion, and an IDH1 R132H mutation was identified by immunohistochemical analysis (Fig. 1D). MGMT promoter methylation testing was negative. An integrated diagnosis of astrocytoma, IDH mutant, CNS WHO grade 4 was made. The resection was followed in March by standard-of-care chemoradiation therapy, consisting of the Stupp protocol, i.e., 6 weeks of radiation (30 fractions of 2 Gy) with concurrent temozolomide (TMZ) at 75 mg/m^2, followed by 6 cycles of adjuvant TMZ at 150 mg/m^2. However, before the end of the year, a CT scan revealed that the tumor had recurred.

The patient was evaluated for participation in the ongoing phase 2a portion of the ongoing IN NEO100 study but was found ineligible because her tumor exceeded 30 mm in size, based on MRI performed in January 2023 (Fig. 2). However, she was found eligible for IN NEO100 under the RTT pathway, and intervention with 288 mg 4 times per day NEO100 was initiated 4 weeks later. To confirm the biological uptake of IN NEO100, serum was drawn from the patient shortly after the administration of the first dose on day 1. Pharmacoanalytical measurements for POH and its main metabolite, perillic acid (PA), were performed. As shown in Fig. 3, both molecules were readily detectable, confirming biological uptake of the drug.

The patient continued to self-administer IN NEO100 during all of 2023 and into 2024. During this time, regularly obtained MR images revealed slow but continuous tumor regression. Representative images (Fig. 2) showed a decrease in signal intensity at the lesion site over the course of 4, 11, and 13 months. Strikingly, at 13 months after the start of NEO100, the previous enhancement at the tumor site had disappeared, suggesting that the tumor had regressed below the detection limit of MRI.

Along with these apparent reductions in tumor size, the frequency of seizures and the level of anxiety decreased, so that the use of antiseizure and anxiolytic medications (gabapentin, levetiracetam, alprazolam, and duloxetine) could be tapered down. Moreover, no serious side effects of NEO100 were noted, altogether emphasizing that quality of life improved and remained high during this long-term treatment regimen.

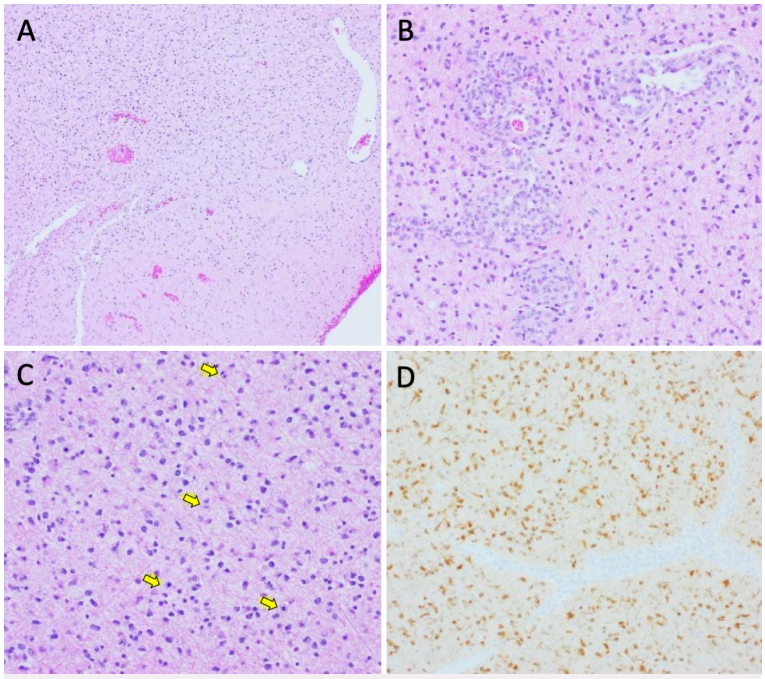

FIG. 1. Neuropathological photomicrographs of resected tissue and IDH1 staining. An infiltrative glial neoplasm was identified, with a clear cellular gradient (**A**) visualized. Microvascular proliferation (**B**), a histologically high-grade feature, and elevated mitotic activity (**C**, *yellow arrows*) were present, amid neoplastic glial cells with enlarged, irregularly shaped nuclei. Immunohistochemistry was positive for the IDH1 p.R132H mutation, indicated by brown cytoplasmic staining (**D**). Hematoxylin and eosin (A–C). Original magnification ×40 (A), ×10 (B), ×200 (C), and ×100 (D).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

Recurrence in malignant glioma is almost universally anticipated, and no effective treatments exist once standard chemoradiation therapy has failed. We are investigating NEO100, which is administered on a daily basis, 4 times per day, via IN delivery, as a novel approach to potentially improve on these dismal outcomes. In an earlier case study,[28] we were able to demonstrate the presence of both POH and its metabolite PA in resected brain tumor tissue of a patient with recurrent GBM who took a dose of IN NEO100 shortly before surgery. This finding confirmed that the IN delivery method indeed is able to deliver the active pharmacological agent to its intracranial target. In the current case study, the patient was not scheduled for repeat surgery and therefore no glioma tissue was available for pharmacoanalysis; however, a blood draw after IN NEO100 delivery enabled us to readily confirm the biological uptake of NEO100/POH in this patient. These results are in pronounced contrast to earlier phase 1 and 2 clinical trials using an oral formulation of POH that failed to detect the presence of POH in patient blood samples, despite administering significantly higher amounts of this compound.[11,12] In retrospect, it appears consistent that therapeutic activity in response to oral POH could not be established.[7–9]

A previously completed phase 1 trial with IN NEO100 demonstrated its exceptional safety when administered daily over many months.[23] Preliminary analysis of efficacy in the 12 patients of that trial suggested that the greatest benefit might unfold in patients harboring IDH mutations in their tumor tissues, and the case presented in the current report adds further compelling evidence to this notion. In the case presented here, the patient showed remarkable tumor regression, where after 13 months of daily IN NEO100, no obvious signs of the tumor remained. This positive development was accompanied by the better management of seizures, along with an overall improvement in functional status and quality of life. Over the course of the treatment, the patient was able to taper down the use of antiepileptic drugs, which is a rare occurrence in patients with brain tumor–related epilepsy.[29] As seizures in themselves carry an intrinsic risk for injury,[30] NEO100 treatment benefited this aspect of quality of life.

The presence of an IDH mutation is known to provide a survival advantage for newly diagnosed patients with grade 4 glioma (astrocytoma vs GBM), but whether there is a better prognosis in the setting of recurrence is less clear. The mOS for newly diagnosed grade 4 astrocytoma, which by definition is IDH mutant, is about 31 months,[31] whereas the mOS for newly diagnosed GBM, which by definition is IDH wildtype, is about 15 months.[32] In the recurrent setting (first recurrence only, as it applies to our patient), mOS was reported in the 12- to 20-month range for grade 4 astrocytoma and in the 6- to 9-month range for GBM.[10,33,34] However, a study by Tabei et al.[35] determined mOS at 10.1 months for grade 4 astrocytoma (n = 13) and 10.5 months for GBM. It is quite likely that additional molecular expression profiles, along with microenvironmental conditions, play a critical role in shaping the survival of these patients. One such critical component is MGMT.

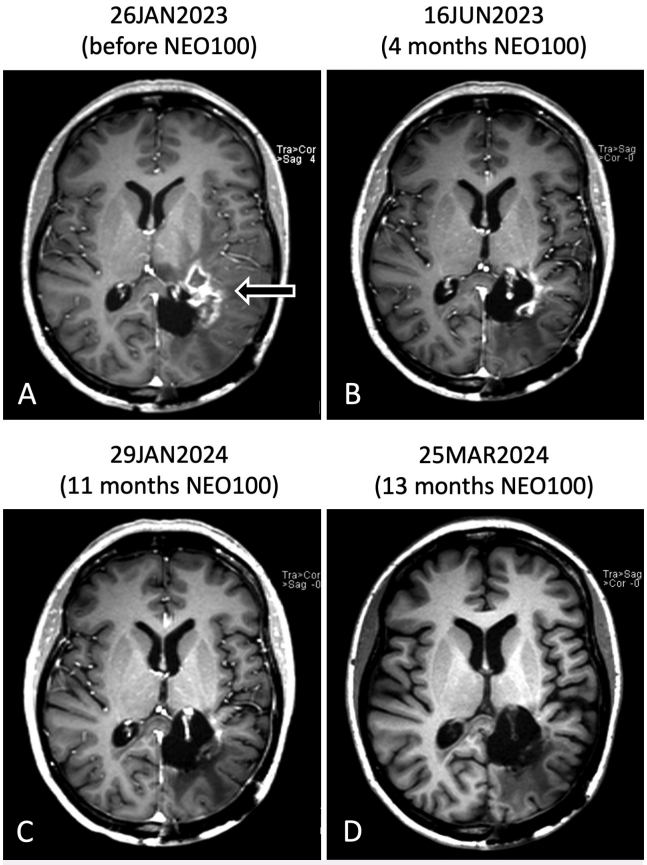

FIG. 2. Postcontrast T1-weighted 3D spoiled gradient recalled echo (SPGR) images were obtained. **A:** After recurrence, a baseline study before the onset of treatment with NEO100 (January 2023). The tumor burden appears adjacent to the resection cavity (*arrow*) and was 3.7 × 2.8 × 4.6 cm in size. **B:** At 4 months after the initiation of treatment (June 2023), there appears to be less size at the location of tumor recurrence. **C:** At 11 months (January 2024), tumor tissue size is further reduced. **D:** At 13 months (March 2024), there is no apparent nodular enhancement at the location of tumor recurrence. These findings are consistent with disease remission, by both the MacDonald and RANO (Response Assessment in Neuro-Oncology) criteria.

It is noteworthy that our patient's tumor harbored an unmethylated MGMT promoter, indicating the presence of MGMT protein in the tumor cells. MGMT is well known to remove the methyl moiety placed onto the O^6-position of guanine by the alkylating function of TMZ, thereby neutralizing the cytotoxic impact of the drug and making the tumor resistant to TMZ.[36–38] In our patient, this process quite likely contributed to her relatively early recurrence after chemoradiation therapy with TMZ. A recent study[31] retrospectively analyzed the survival of patient cohorts (n = 133) with the same initial diagnosis as our patient—astrocytoma, IDH mutant, CNS WHO grade 4—who mostly were treated with resection, followed by the Stupp protocol. The authors determined that the mOS was 40.7 months for those patients with a methylated MGMT promoter, but only 18 months for those with an unmethylated MGMT promoter. Early recurrence in our patient, therefore, was in line with the dismal prognosis expected from MGMT unmethylated disease. Worsening our patient's prognosis further was the fact that early recurrence usually indicates accelerated progression and shortened survival in IDH-mutant gliomas.[39,40]

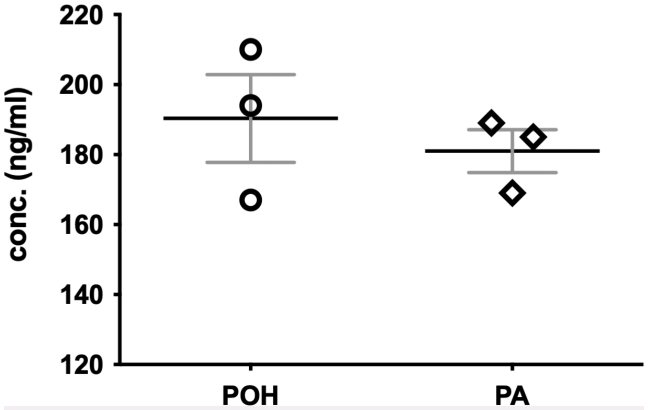

FIG. 3. Serum concentration (conc.) of POH and PA after IN NEO100. Five minutes after IN administration of 1 dose of NEO100 (288 mg), the patient's blood was drawn. The plasma was analyzed for the presence of POH and PA, the main metabolite of POH. The analysis was performed in triplicate; shown are the individual data points for each molecule, along with the mean and standard deviation. Measurements were performed using high-performance liquid chromatography coupled with UV detection.[41]

Lessons

Our case study presents an example showing that IN NEO100 was well tolerated and correlated with tumor regression. Despite unfavorable conditions, such as early recurrence, unmethylated MGMT promoter, and large size of the recurrent tumor mass, there was striking tumor regression upon IN NEO100 treatment, and at present the patient has surpassed the expected mOS mark of 18 months (since the initial diagnosis) by a significant margin and in good health, without adverse and unanticipated events. These results further support the notion that the novel conceptual approach of IN NEO100 has the potential to become a clinically beneficial regimen for the improved treatment of recurrent astrocytoma, IDH mutant, CNS WHO grade 4. Naturally, as a case study, our report is limited by n = 1; large clinical trials, such as the currently ongoing phase 2 study, are necessary to measure the efficacy of the IN approach with NEO100.

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Disclosures

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Conception and design: Chen, Schönthal, Senecal. Acquisition of data: Chen, Swenson, Mittenzwei, Go. Analysis and interpretation of data: Chen, Schönthal, Swenson, Mittenzwei, Go. Drafting the article: Schönthal, Mittenzwei. Critically revising the article: Chen, Schönthal, Go. Reviewed submitted version of manuscript: Schönthal, Swenson, Senecal, Go. Approved the final version of the manuscript on behalf of all authors: Chen.

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