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Intravenous Honokiol in Drug-Resistant Cancer: Two Case Reports

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Abstract

Context: Long-term patient survival in cancer is affected by drug resistance. Honokiol (HNK) is a small-molecule polyphenol isolated from the bark and seed cones of *Magnolia officinalis*. HNK has been shown to enhance the effects of chemotherapy and inhibit drug resistance in preclinical models. HNK was well tolerated in multiple animal models when administered orally, intravenously (IV), and via intraperitoneal route. However, there are limited human data on the use of HNK in general, and specifically via IV (HNK-IV) in cancer. **Objective:** We aim to assess the efficacy, safety, and tolerability of HNK-IV in patients with drug-resistant tumors. **Methods:** This is a case study of 2 cancer patients who utilized HNK-IV as part of their cancer treatment regimen. The initial infusion of HNK was 10 mg/kg body weight, and subsequent treatments were increased up to 50 mg/kg according to individual tolerance, over 2 weeks. **Results:** Positive clinical response was achieved in both patients, including improved symptoms and quality of life. No serious adverse side effects occurred, and there were no adverse effects on laboratory parameters (complete blood count, kidney, and liver function). Transient sedation and minor nausea were noted and resolved postinfusion. **Conclusions:** This is the first report of HNK-IV in human patients. Given the positive clinical results, safety, and tolerability, the use of HNK-IV warrants further investigation regarding optimum formulation, and its use as adjunctive therapy in cancer patients.

Keywords

polyphenol, magnolia, adjuvant therapy, mTOR, NF-κB, p53

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Introduction

The metastatic spread of solid tumors is responsible directly or indirectly for most cancer-related deaths.[1] Although many tumors are treatable if detected early, drug resistance and tumor recurrence are common obstacles to long-term patient survival. According to the American Cancer Society (ACS), the metastatic prostate cancer 5-year relative survival rate is 30%.[2] Also, ACS sets the 5-year survival rate for localized triple-negative breast cancer at 91%.[3] However, an individual's outlook depends on many factors, including the stage of cancer and the grade of the tumor.[4] Combination therapies, including naturally occurring agents that could serve as adjuncts to conventional treatments, can play an essential role in cancer treatment.

Honokiol (HNK; 3′,5-di-(2-propenyl)-1,1′-biphenyl-2,2′-diol) is a bioactive polyphenol isolated from the bark and seed cones of *Magnolia* spp, a plant with a long history of use in traditional Asian medicine. A large body of preclinical research indicates that HNK modulates numerous intracellular signaling pathways involved with cancer, including nuclear factor-κB (NF-κB), signal transducers and activator of transcription 3 (STAT3), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR). HNK also has been shown to block signaling in tumors with defective p53 function.[5,6]

Honokiol has been demonstrated to enhance the effectiveness of chemotherapy drugs and to inhibit drug resistance through the downregulation of p-glycoprotein in a variety of preclinical models.[5-13] For example, HNK is beneficial with etoposide at inducing apoptosis in human breast cancer cells[7]; cisplatin in vivo in ovarian and colon cancer xenograft models[8,9]; docetaxel in prostate cancer cells[10]; doxorubicin in doxorubicin-resistant uterine sarcoma cells[11]; and paclitaxel in a drug-resistant human cancer

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model.[12] The inhibition of NF-κB may be the dominant mechanism responsible for these effects.[10]

Honokiol was well tolerated in multiple animal models when administered orally,[14] intravenously (IV),[15] and via intraperitoneal route.[8] This report aims to assess the safety, tolerability, and efficacy of HNK-IV in 2 drug-resistant cancer patients, as determined by clinical observation.

Patients and Methods

Population

This case study report includes 2 oncology patients being treated adjunctively at the Amitabha Medical Clinic and Healing Center (Amitabha Medical Clinic, Santa Rosa, CA) by the attending physician, Dr Isaac Eliaz. The patients had documented cancer, no known allergies to HNK, tolerance to an oral test dose, and tolerance to other prior intravenous treatments. Patients signed written informed consent for experimental treatment with HNK-IV, and patient or proxy consent for publication of case studies was obtained.

Materials

HNK-IV was prepared at an accredited compounding pharmacy under sterile conditions and tested for sterility, potency, and identity. The 98% HNK was tested for purity (ChromaDex, Irvine, CA). The HNK-IV formulation included >98% HNK at 50 mg/mL, ethyl alcohol (Letco Medical, Inc, Decatur, AL) at 100 mg/mL, and polysorbate 80 (Letco Medical, Inc) at 80 mg/mL, in sterile water (single-use 50 mL vial). The HNK-IV preparation was mixed in 250 mL 5% dextrose solution immediately prior to IV administration.

Dosing

After a 24-hour observation period following the successful administration of an oral test dose of HNK (250 mg capsule; 98% HNK), the patients received an initial dose of 500 to 750 mg HNK equaling 10 mg/kg body weight, administered intravenously over 45 to 60 minutes with close monitoring. Following successful administration, the dose was escalated on an individual basis over a 1- to 2-week period, to a maximal dose of 50 mg/kg.

Safety, Tolerability, and Efficacy

Safety was evaluated with ongoing monitoring of complete blood counts and comprehensive metabolic panels. The response was assessed through clinical evaluation, laboratory testing that included serum tumor markers, as well as periodic imaging performed at intervals determined by the treating oncologist (who did not administer the HNK-IV). Tolerability was evaluated by ongoing clinical evaluation by the attending physician and the nursing staff. The assessment included treatment-related effects reported during and following treatment, between treatments, as well as changes in morbidity and functionality.

Results

Case 1

A 69-year-old male diagnosed in 2004 with prostate cancer, 1 year before being seen at Amitabha Medical Clinic. At the time of diagnosis, the patient had a prostate-specific antigen (PSA) of 62.8 ng/mL; Gleason score of 3 + 3; T4, N1 tumor with perineural invasion; and extensive pelvic lymphadenopathy per magnetic resonance imaging.

The patient chose not to pursue conventional therapies, adopting a macrobiotic diet instead. This approach resulted in a fall in PSA to 38.5 ng/mL, followed by a slow ascension with a PSA zenith at 3 years postdiagnosis of 122 ng/mL, accompanied by pelvic bone metastasis. At this time, in August 2005, he presented to Dr Isaac Eliaz at Amitabha Medical Clinic. In addition to ongoing integrative therapies at Amitabha Medical Clinic, the patient was started on androgen deprivation therapy using bicalutamide followed by leuprolide, with good response, and subsequent PSA falling to 0.2 ng/mL.

Over time, the patient developed a castrate-resistant disease, and the skeletal metastases continued to progress. In the summer of 2013, he started chemotherapy treatment at Compassionate Oncology in Los Angeles. Under their care, the patient received docetaxel, carboplatin, and estramustine, followed by various therapies prescribed at Compassionate Oncology. Following the course of treatments, the patient showed stable osseous metastases per scans with PSA at 6.0 ng/mL. At that time, the patient continued his androgen deprivation therapy protocol that included a combination of leuprolide, enzalutamide, metformin extended release, and celecoxib.

The patient presented with a seizure in November of 2014 and was diagnosed with grade II astrocytoma, not amenable to resection. The patient declined surgical and chemotherapeutic interventions for his astrocytoma, as well as antiseizure medications. He had ongoing complex partial seizures, with symptoms of grimacing from foul taste and smell. In 2015, the PSA began to climb from a low of 2.1 ng/mL in July of 2014 to 10.99 ng/mL in March of 2015, to 16.45 ng/mL in June of 2015, and to a high of 147.9 ng/mL in November of 2015. Significant clinical deterioration was seen with increased bone pain, weakness, and difficulty with motility and walking. The patient was still taking leuprolide throughout this time and continued taking it until shortly before his death. His condition continued to deteriorate through January 2016. At that time, the patient was

house-bound and nearly bedridden. Following a home visit by Dr Eliaz, HNK-IV therapy commenced. The initiation of HNK-IV occurred on January 19, 2016. An initial dose of 10 mg/kg was increased over 2 weeks to 30 mg/kg, 3 times a week on an ongoing basis when HNK-IV was available. The patient had clinical improvement with a reduction in pain, improved mobility, energy, and appetite, and cessation of partial olfactory seizures.

Follow-up PSA in February of 2016 declined to 68.5 ng/mL, showing stabilization through August of 2016 at 79.5 ng/mL. The patient stopped the HNK-IV during the summer of 2016 due to supply shortage, resulting in worsening of the partial olfactory seizures and other symptoms. Eventually, the PSA progressively increased to a high of 184 ng/mL in January of 2017. At this time, HNK-IV was restarted at a dose of 30 mg/kg, 3 times a week. PSA decreased to 66.8 ng/mL in July of 2017, accompanied by improvement in symptoms. The patient was able to leave his home and take short walks. Due to difficulties in obtaining HNK-IV, the dose was reduced to only one IV a week starting in August of 2017 and discontinued in December of 2017 due to lack of availability.

Treatment response to HNK-IV included effective control of seizure symptoms, reduced bone pain, and improved quality of life for 22 months. HNK-IV was tolerated well without adverse symptoms either during or following treatments. The patient was able to rest comfortably during the infusions, with improvement in pain control. These benefits lasted during the interim periods between treatments. Following the discontinuation of the HNK-IV therapy, the patient continued to deteriorate and passed away in April of 2018.

Case 2

A 59-year-old female diagnosed with triple-negative IIA (T1a node-negative, grade 3/3) infiltrating ductal breast carcinoma in May of 2013. The patient was receiving chemotherapy at a local oncology office while receiving integrative care by Dr Eliaz at Amitabha Medical Clinic, where she is still receiving integrative care to date. Between the time of diagnosis and commencement of neoadjuvant chemotherapy 10 weeks later, the tumor size assessed by ultrasound showed an increase in lesion dimensions, from 16 × 19 × 14 mm to 23 × 18 × 23 mm. The patient's pathology slides were sent for Caris Molecular Intelligence testing (Caris Life Sciences, Irving, TX). The patient received neoadjuvant chemotherapy at a local oncology center in Santa Rosa, California. She completed 4 cycles of 5-fluorouracil/epirubicin/cytoxan (FEC) with partial response and residual tumor present in both physical examination and imaging.

Following FEC, the patient began docetaxel treatment. After 1 round, there was clear evidence of disease progression in physical examination. Magnetic resonance imaging revealed a well-circumscribed mass (4.1 × 3.8 × 3.4 cm) that had increased in size from the initial scans prior to the commencement of the neoadjuvant chemotherapy. Laboratory data revealed cancer antigen (CA) 15-3 levels of 28.6 U/mL, compared with 7.6 U/mL at the start of chemotherapy, both within the normal range (0.0-35.0 reference range). At that time, due to the progression under docetaxel and the Caris Molecular Intelligence results that showed sensitivity to carboplatin and gemcitabine, the patient's neoadjuvant chemotherapy was changed by her treating oncologist to carboplatin and gemcitabine for 4 cycles. At the end of the third cycle, and before the administration of the fourth and last cycle, the tumor was still clinically palpable and estimated at 2 to 3 cm, indicating only a partial response. HNK-IV was initiated with the fourth chemotherapy cycle, at an initial dose of 10 mg/kg, increased to 40 mg/kg 5 days later, and continued at the same dose of 40 mg/kg, 3 times a week, for a total of 7 treatments over 3 weeks (treatment 1 on week 1, treatments 2, 3, and 4 on week 2, and treatments 5, 6, and 7 on week 3). During HNK-IV treatment, the tumor became nonpalpable, and the CA 15-3 levels fell to 14.5 U/mL. Partial mastectomy performed post neoadjuvant chemotherapy revealed a 0.3-cm residual tumor, with 2 negative sentinel lymph nodes. Postsurgical radiation therapy was administered. Posttreatment positron emission tomography/computed tomography (PET/CT) revealed no hypermetabolic activity or indications of active neoplastic disease. The patient has had no recurrence and continues to be disease-free 5 years after the completion of treatments.

Adverse Effects

HNK-IV was tolerated well in both cases, with no serious adverse effects. The most frequently reported side effect was transient sedation, which resolved posttreatment. Other reported side effects were dry cough, temporary low back pain, mild dizziness, and paresthesia; all adverse effects resolved quickly with rate reduction during administration or posttreatment. Nausea was reported infrequently and resolved within several hours. Neither patient discontinued therapy due to the adverse impacts. Hematological values remained stable, with no treatment-related adverse events.

Discussion

To our knowledge, Amitabha Medical Clinic and Healing Center is the first and currently the only medical center that has offered HNK-IV treatment. This report of the first clinical use of HNK-IV provides evidence of possible benefit in cancer patients. The 2 cases presented here suggest that HNK-IV exhibits independent antitumor activities and may enhance the effectiveness of standard treatments, consistent with previous reports.[5-12] HNK influences a large number of

signaling pathways that promote apoptosis and inhibit angiogenesis, which might account for its ability to affect multiple cancer types.[5,6] HNK-IV was safe and well tolerated and did not appear to interfere with other therapies.

Case 1 had significant clinical improvement with the introduction of HNK-IV, with a reduction in pain, improved mobility, energy, and appetite, and cessation of partial olfactory seizures. After stopping the HNK-IV for 6 months, his PSA rose from 79.5 ng/mL in August of 2016 to 184 ng/mL in January 2017. Once the HNK-IV treatment recommenced, the PSA dropped to 66.8 ng/mL in July of 2017, accompanied by improvement in symptoms and quality of life.

In case 2, FEC neoadjuvant therapy had a partial response by clinical observation. Docetaxel treatment then failed the patient, who showed a progression of tumor size and an increase in CA 15-3 levels (but still within the normal range). After the failure of the docetaxel, the patient was switched to a carboplatin-gemcitabine regimen and completed 4 cycles of this regimen. Prior to the fourth cycle, the tumor was still palpable and estimated to be 2 to 3 cm in size, based on physical examination. HNK-IV was initiated with the fourth cycle of carboplatin-gemcitabine treatment and continued throughout the fourth cycle. The tumor became nonpalpable during the fourth cycle, and the CA 15-3 levels dropped. The shrinkage of the tumor could have been due to the carboplatin-gemcitabine treatment alone, the HNK-IV alone, the combination of the two, an anti-inflammatory response initiated by HNK-IV, or a potential placebo effect. While the patient is alive and cancer-free for over 5 years posttreatment, such results are not unexpected.

In preclinical animal models, HNK is effective against a broad range of drug-resistant cell lines and tumors, including cervical cancer,[7] sarcomas,[11] and breast cancer.[12] The current observations in humans may be consistent with these preclinical studies. Case 1 had prostate cancer that showed resistance to hormonal therapy. There also might have been resistance to docetaxel in case 2. HNK-IV exhibited possible anticancer benefits in these patients. Additional benefits in symptom control were seen particularly for case 1, who received HNK-IV over an extended period, with effective reduction in seizure activity, as well as pain control for the osseous metastases. As noted previously, HNK is known to cross the blood-brain barrier[15] and shown to have benefits in astrocytomas/glioblastomas.[16] This may warrant additional clinical investigation for potential adjunctive use in the treatment of glioblastomas.

Importantly, there were no severe side effects that required treatment discontinuation. HNK-IV was well tolerated, which allowed for higher dosing compared with oral administration.

This case study is the first report of the adjunctive use of HNK-IV in humans with solid tumors. The individual cases of the 2 patients demonstrated that HNK-IV may exhibit anticancer activity or may work additively or synergistically with other medications in drug-resistant/hormone-resistant tumors. The preliminary findings suggest that the use of HNK-IV as an adjunctive therapy could be safe and beneficial. Further investigation into the optimum formulation of HNK-IV and its use as adjunctive therapy in cancer patients is warranted.

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