CASE REPORT

Control of Metastatic Tumor Growth in a Patient with Sporadic Metastatic Malignant Peripheral Nerve Sheath Tumor (sMPNST) Using the Hope Alternative Treatment Cancer Protocol

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ABSTRACT
Metastatic sporadic malignant peripheral nerve sheath tumor (sMPNST) is associated with only 17% five-year survival rate using standard chemotherapy and there are no 10-year survival reports with the exception of a case report wherein a patient with metastatic sMPNST is still alive with no active disease and on no further cancer therapy, >12 years from DeltaRex-G treatment initiation. In this case report, we describe an interim alternative treatment regimen designed and used by a patient with metastatic sMPNST, while awaiting the return, GMP bioproduction, and QC certification of DeltaRex-G as a potential treatment option. We report on the successful control of metastatic tumor growth over a one-year treatment period using the Hope Protocol consisting of artemisinin, curcumin, cannabis oil, disulfiram, fenbendazole, mebendazole, albendazole, atorvastatin, doxycycline, vitamin C, vitamin E, a plant-based diet, sans refined sugar, yoga, acupuncture, meditation, exercise and hot sauna, and we discuss their biochemical mechanisms of action.

KEYWORDS: Integrative cancer therapy; Repurposed drugs; DeltaRex-G gene therapy.

INTRODUCTION
Malignant peripheral nerve sheath tumors (MPNSTs) are a rare, aggressive, and deadly subtype of soft tissue sarcomas (STS) wherein disease management upon surgical resection remains a challenge with poor prognosis due to a diversity of metastatic karyotypes, a multiplicity of signaling pathways, a dismal drug response rate, and a lack of durable clinical responses. The medical oncologist’s quest for a “druggable” locus or a biochemical pathway for control of tumor growth is a long-standing goal of Precision Medicine: supported by the development, clinical performance, and demonstrated survival value of DeltaRex-G (formerly Rexin-G), prompting its regulatory revival and recent return to the cancer clinic under the “The Blessed Protocol”: Expanded Access for DeltaRex-G for Advanced Pancreatic Cancer and Sarcoma, NCT04091295. Opened February 2020. Metastatic sporadic malignant peripheral nerve sheath tumor (sMPNST) is associated with a poor prognosis with a 17% five-year survival using the best-known treatment including surgery, radiotherapy, and chemotherapy. Frequently used chemotherapeutic agents include anthracyclines, ifosfamide, cisplatin, and etoposide, with anthracycline plus ifosfamide, followed by ifosfamide plus cisplatin plus etoposide as the most common treatment regimens.1 Ten-year survival rates have not been reported for metastatic sMPNST with the exception of a case report wherein a patient with metastatic sMPNST is still alive with no active disease and on no further cancer therapy, >12 years from DeltaRex-G treatment initiation.2
In this report, we describe an alternative treatment regimen designed and used by a patient with metastatic sMPNST, discuss the anti-cancer properties of re-purposed drugs and their mechanisms of action, as well as the positive effects of yoga, acupuncture, meditation, exercise and hot sauna which were incorporated in this alternative treatment program.

CASE REPORT
This is a 27-year-old white female who was diagnosed with grade 3 malignant peripheral nerve sheath tumor (MPNST) of the left parapharyngeal space in December 2014. On 12/6/2014, patient underwent a near total transcervical tumor resection with residual internal carotid artery disease. From 1/2015 to 4/2015, she received 6 cycles of doxorubicin + ifosfamide. Patient also completed 66 Gy in 33 fractions on 7/24/2015 in an adjuvant setting. In 10/2015, a metastatic deposit in the left carotid artery outside the radiotherapy field was noted and in 12/20/2015, resection of the carotid metastasis and en-bloc lymph node resection was done. From 2/24/16 to 4/6/16 patient received 60 Gy in 30 fractions. Follow-up CT scan on 12/14/18 demonstrated enlarged 2.3 cm right hilar (SUV = 4.7) node and a subcarinal node (SUV = 2.5) as well as multiple sub-centimeter pulmonary nodules. The patient was seen at Sloan Kettering Memorial Hospital where a pathology review revealed metastatic high-grade spindle cell sarcoma with a 60% PD-1 positivity. She was then seen at the Cancer Center of Southern California/Sarcoma Oncology Research Center, Santa Monica CA for a second opinion in January 2019. At that time, the pulmonary nodules had grown slightly bigger and she was advised to participate in an on-going Phase 2 clinical trial using trabectedin, ipilimumab and nivolumab for soft tissue sarcoma. However, the patient refused to take any more chemotherapy and wanted to try DeltaRex-G for soft tissue sarcoma. While waiting for DeltaRex-G, the patient started on a self-designed alternative treatment regimen beginning in February 2019, consisting of cannabis oil 60% CBD:40%THC (3:2), plant-based diet, no refined sugar, fenbendazole 500 mg/day, mebendazole 250 mg/day, vitamin E supplement 3 tablets/day, and atorvastatin 40 mg/day. Additional procedures included yoga, acupuncture, meditation, exercise, and hot sauna.

Rationale and Mechanisms of Action:
The following rationale and mechanisms of action form the basis of the individual treatments and procedures:

Cannabis oil
Two representative exogenous cannabinoids from Cannabis sativa, cannabidiol (CBD) and D9-tetrahydrocannabinol (D9-THC) have been tested in combination as a potential treatment of cancer. Various proposed mechanisms of action include cell cycle arrest, induction of apoptosis, as well as inhibition of neovascularization, migration, adhesion, invasion, and metastasis. Specifically, CBD inhibits the PI3K/AKT survival pathway by inhibiting phosphorylation of AKT1/2 (pAKT) and p42/44 MAPKs without affecting the total AKT and p42/44 MAPK protein levels. In breast cancer, cannabis oil inhibits Akt and mTOR signaling, resulting in apoptosis and autophagia, a self-degradative process that is becoming increasing important in cancer therapy. CBD exerts its effects on MCF-7 through cell cycle arrest at the G1/S checkpoint. In prostate cancer cells, cannabis oil decreases androgen receptor (AR) mRNA expression as well as expression of CB1 and CB2 resulting in decreased cell viability. Despite the multitude of positive results with D9-THC-related cannabinoids in cancer research, the clinical use of these compounds is limited due to their psychoactive side effects.

Plant-based diet
A plant-based eating pattern focuses primarily on foods derived from plants—i.e., vegetables, fruits, nuts, seeds, oils, beans, legumes, and whole grains. Plant-derived foods provide thousands of phytochemicals—including dietary fiber, carotenoids, dithioliones, isothiocyanates, flavonoids, and phenols, which have demonstrated anti-cancer effects in cell and rodent studies. They are also a rich source of various nutrients that can impact cancer risk, such as vitamins C and E, selenium, and folate. A substantial body of experimental data links many of these compounds with anti-tumorigenic effects in various cells in both animal and in vitro models.

In a large study of combined data on US and Chinese women, ingesting soy food of >10 mg isoflavones/day after diagnosis of breast cancer was associated with a statistically significant reduced risk of recurrence. One of the studies included in the After Breast Cancer Pooling Project, the Women’s Healthy Eating & Living Study, was registered at clinicaltrials.gov as NCT00003787.

Project, the Women’s Healthy Eating & Living Study, was registered at clinicaltrials.gov as NCT00003787. One reason for the use of plant-based diet especially soybean products is that the isoflavones found in soybean and soybean products have the ability to reactivate BRCA genes, therefore increasing DNA repair and decreasing the odds of developing breast cancer. One reason for eliminating meat in the diet is that the increased 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) in cooked meat has an estrogen-like effect causing cell growth and development of breast cancer.

Restriction in refined sugar intake
Sugar from any source is a simple carbohydrate that the body converts into glucose, a central nutrient that is used in several metabolic pathways but is consumed by tumors at exceptionally high levels to support their growth. Refined, or extracted, sugars are metabolized more quickly than naturally occurring sugars, causing insulin and blood sugar levels to spike (hyperglycemia). Intermittent and chronically elevated levels of this state have been shown to stimulate oncogenesis, inhibit apoptosis, promote metastasis and tumor cell resistance to radiation and chemotherapy.

Further, increased blood glucose levels lead to increased insulin levels in the circulation with subsequent increase in insulin growth factor (IGF). This in turn activates the mammalian target of rapamycin (mTOR), resulting in cell growth and oncogenesis. Decreased sugar intake activates AMPK, which inhibits mTOR resulting in apoptosis and autophagy.

Atorvastatin
Statins are among drugs that have been shown to possess...
apoptosis-inducing effects. Statins induce apoptosis in cancer cells directly via the inhibition of hydroxymethylglutaryl coenzyme A reductase (HMGCR) activity.

Disulfiram
Disulfiram increases copper uptake, which induces reactive oxygen species causing DNA damage and activation of p53 signaling resulting in tumor suppression.

Fenbendazole
Although the exact mechanism of action is unknown, it is thought that fenbendazole disrupts the microtubule system, stabilizes p53 and interferes with glucose metabolism resulting in elimination of cancer cells.

Mebendazole
In non-small cell lung cancers and gastric cancers, mebendazole works by tubulin polymerization, causing cell cycle arrest. Furthermore, mebendazole sensitizes cancer cells to radiotherapy by inhibiting proteins responsible for DNA repair.

Albendazole
Albendazole causes cell death via apoptosis-mediated pathways hence inhibiting growth of head and neck squamous cell carcinoma.

Doxycycline
Doxycycline exerts its effect by inhibiting mitochondrial protein synthesis, resulting in decreased energy, inhibition of cell proliferation, clonogenicity, invasion, and migration.

Artemisinin
Artemisinin reacts with iron-forming free radicals which mediates cellular damage and apoptosis of cells such as cancer cells with high iron levels. A specific dosage has not been established; however, 400-800 mg per day for 6 to 12 months have been shown to be useful.

Curcumin
When combined with chemotherapy (cisplatin, docetaxel, doxorubicin, 5-flourouracil), high dose curcumin enhances synergism by modulating signaling proteins: Akt, MMP2/9 (matrix metalloproteinase), mTOR and VEGF (vascular endothelial growth factor) in Hodgkin lymphoma, gastric, hepatocellular bladder, colorectal and prostate cancers.

Vitamin C
Vitamin C role upregulates autophagy markers, Beclin-1, and LC3B-II proteins, inducing cell death in human hepatocellular carcinoma cells. In addition to autophagy, Vitamin C induces DNA damage and ATP depletion, causing apoptosis and cell death via cell cycle arrest.

Vitamin E
Vitamin E blocks cancer-promoting pathways such as cyclooxygenase and 5-lipoxygenase resulting in inhibition of cellular proliferation and cancer cell death.

Yoga
In an electronic database search (PubMed) through December 2016, 138 clinical trials with a total of over 10,000 cancer patients from 20 countries reported that yoga improved the physical and psychological symptoms, quality of life, and markers of immunity of cancer patients, providing a strong support for yoga's integration into conventional cancer care.

Yoga reduces stress hormones, improves parasympathetic function, and increases relaxation. By changing perception and reactivity to situations, one can reduce anxiety resulting in improved sleep and enhanced immune response. Further, hypoxia enhances malignant potential of tumor invasion and metastasis. Yogic postures and breathing techniques focus on improving both lung and heart functions therefore increase oxygen saturation and decreases malignant potential.

Meditation
Meditation has been widely shown to reduce physiological markers of stress, including cortisol and tumor necrosis factor alpha, in a range of populations. Cortisol suppresses immune function when it is present in high amounts, causing NK cell activity to decrease by up to 50 percent. Elevated cortisol over the long term consistently produces excess glucose, leading to increased blood sugar levels and insulin resistance, thus fueling cancer growth, suppressing apoptosis, and promoting metastasis and tumor cell resistance to radiation and chemotherapy. Cancer impairs cognition, memory, and psychological functions. Practicing mindfulness meditation has been shown to improve cognitive regulation via increased activity in the anterior cingulate and anterior insular cortices. Cognitive modulation improves emotional state and self-awareness.

Exercise
Physical activity improves insulin sensitivity and reduces fasting insulin levels, while its immunomodulatory effects enhance innate and acquired immunity and promote tumor surveillance. Aerobic exercise can decrease oxidative stress and enhance DNA repair mechanisms, decreasing carcinogenesis.

Exercise also blocks adrenergic signaling resulting in decreased catecholamine levels which can reduce the ability of cancer cells to form tumors in distant sites. Furthermore, exercise reduces mTOR signaling thus preventing tumor growth.

Hot sauna
Hot sauna neutralizes HSP70 expression which in turn may sensitize tumor cells to chemotherapy and inhibit tumor growth.

Acupuncture
Cancers impair autonomic functions such as blood pressure, gut motility and immune responses. Acupuncture leads to modulation of the parasympathetic and sympathetic nervous system and thus able to regulate blood pressure, motility and immune responses.

Radiologic imaging and laboratory studies during the treatment period.
Serial CT scans of chest, abdomen and pelvis were obtained during the alternative treatment period from February-December 2019.

RESULTS
Serial CT scans of chest, abdomen and pelvis revealed stabilization/reduction of tumor growth of this high-grade sarcoma over a one-year observation period. Figure 1 shows gradual reduction in the size of the lung nodules up to 27% maximum reduction. Treatment-related adverse events included Grade 1 (mild) hyperchromic macrocytic anemia and transient Grade 1 (mild) liver enzyme (AST) elevation, while the patient enjoyed good quality of life with no symptoms of her metastatic pulmonary disease.
DISCUSSION
In the contemporary era of precision medicine, targeted therapies, immunotherapies, and gene-based therapies have been successfully introduced and approved by regulatory agencies in the US and worldwide, with an appreciable trend away from toxic chemotherapies which may cause secondary malignancy, disabling neuropathy, irreversible organ failure, and poor quality of life. In this regard, alternative treatment programs, either as stand-alone or supplementary to standard cancer therapy, are also gaining increasing popularity in the medical and scientific communities. In lieu of an approved and effective monotherapy for advanced metastatic cancers/sarcomas as shown in Figure 2, is a combinatorial approach using multiple kinase inhibitors: blocking multiple CDKs, for example, with the hope of negatively impacting cMyc expression, activation, or stability, while avoiding off-target toxicities and problematic CSC refractoriness. Alternatively, the mechanisms of action of individual treatments and repurposed drugs used by this MPNST patient have been extensively studied, providing individual rationale for their use. Combining all 13 repurposed drugs and nutrient supplements and five healing procedures would appear arduous for some, but gradual implementation of these treatments is possible.

In retrospect, the DeltaRex-G Rescue Mission of 2019 required the sacrifices of many who harkened to the task and/or provided vital funds needed to reconstitute the DNA plasmids, biochemistries, CMC, cGMP, and FDA regulatory approvals now embodied in the restored DeltaRex-G clinical product. From the beginning, it was an international clinical mission of discovery and collaborative translational research which led to the identification and molecular characterization of CCNG1 (Cyclin G1) knockout, tumor-targeted gene delivery, pioneering clinical studies, purposeful dose escalations, ongoing quantitative analyses, and thus, the clinical development of DeltaRex-G. Indeed, it was in the context of advanced metastatic disease, as metastatic cancers were eradicated and long-term cancer-free survivals were achieved, that the clinical value of (i) Tumor surveillance and (ii) Cyclin G1 blockade (dnG1) were revealed. It was by studying histology of tumors, the reactivation of immune responses, and the eradication of multidrug-resistant cancer stem cells that the mechanisms of DeltaRex-G action: i.e., the blockade of the Cyclin G1 / Cdk1,2,5 / Myc / Mdm2 / p53 Axis of...
CCNG1 is a proto-oncogene promoting stem cell competence and cancer stem cell (CSC) survival, transcriptional regulation and cell cycle progression/division. In opposition, DeltaRex-G tumor-targeted gene vector encoding a cytocidal CCNG1 inhibitor gene (dnG1) blocks the G1 phase of the cell division cycle, causing apoptosis (programmed cell death) of cancer cells and CSCs.

Cancer Stem Cell Competence, was validated clinically as an effective and accessible locus for medical oncology.

In principle, a strategic combination of such alternative treatments could work synergistically with targeted therapies and gene-based therapies, including DeltaRex-G: a tumor-targeted gene vector encoding dnG1, a Cyclin G1 inhibitor construct, which has minimal, if any, side effects, and has evoked remission and long-term (>10-year cancer-free) survival in patients with previously hard-to-treat chemotherapy resistant Stage 4 cancers: including soft tissue sarcoma, MPNST, osteosarcoma, pancreatic adenocarcinoma, invasive breast carcinoma, and B-cell lymphoma. Based upon hard-core molecular-genetic lessons learned in the unforgiving crucible of clinical oncology, we hereby extend a central unifying gene-based theme for medical oncology: The Cyclin G1 / Cdk2 / Myc / Mdm2 / p53 / p18 Hamlet Axis of oncogenes controlling cancer stem cell fate (survival vis-à-vis death by apoptosis) is established conceptually as the “Axis Mundi” of Animal Stem Cell Competence: (i) to guide future molecular oncologists, (ii) to provide diagnostic insights regarding chemo-sensitivity and chemo-resistance, (iii) to develop more rational combinatorial therapies alongside evidence-based alternative therapeutic approaches, and (iv) to serve as a bulwark against profuse profiling and molecular occultism.

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The authors declare no competing interests with this case.

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PATIENT’S CONSENT
Written informed consent was obtained from the patient for the publication of this case report.
REFERENCES


