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Original paper

Dose dependent effects of O2/O3 therapy on PSA levels of patient with risk of prostate cancer

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Abstract

Oxygen/Ozone (O_2/O_3) is a complementary therapy for prostate cancer, as with other types of cancer, *i.e.*, it is used in support of conventional treatments such as radiation therapy or surgical removal of the prostate. However, some prostate cancer patients elect to manage prostate cancer by active surveillance rather than conventional therapies in accordance with treatment guidelines, or due to the uncertain prognostic value of testing and the side-effects of the treatments. The objective of this report is to demonstrate the potentially beneficial therapeutic value of O_2/O_3 treatment, applied in effective doses, for a prostate cancer patient electing disease management by active surveillance.

The subject was a 64-year-old male diagnosed by needle biopsy with localized prostate cancer classified as being in the unfavorable intermediate risk group. He elected active surveillance to manage his cancer instead of recommended conventional therapies and received O_2/O_3 therapy for about a year. The treatment was divided roughly into four quarterly phases, with a PSA test performed at the end of each of the four phases. During phases 2 and 3 of the treatment, the patient's PSA score increased from 9.7 ng/mL to 14.7 ng/mL. However, at the end of phase 4 his PSA score decreased to 11.7. During phase 4, the O_2/O_3 treatment was performed more regularly than during phases 2 and 3, and at lower concentrations and overall doses. This suggests that O_2/O_3 treatment at the correct doses and frequency of treatment may have beneficial therapeutic value for a prostate cancer patient electing disease management through active surveillance rather than conventional treatment.

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Introduction

According to the American Cancer Society, in 2019 an estimated 186,290 new cases of prostate cancer were diagnosed in the United States, making this disease the most common solid tumor in men. Despite the high incidence, only 31,620 men are estimated to have died of prostate cancer in 2019. The 10-year relative survival rate is 98%.[1] Prostate cancer arises from genetically altered prostate epithelium and slowly progresses over several decades. Given its features of multifocality and tumor heterogeneity, the course of prostate cancer is difficult to predict.[2] Men may live their entire natural life without having any symptoms from prostate cancer.[2]

The management options for localized prostate cancer include radiation therapy, surgery, and active surveillance. The decision on how to manage prostate cancer in a newly diagnosed patient is quite complex and filled with controversy. Generally, active surveillance is recommended for patients with low grade (no Gleason pattern 4 or higher) and low volume disease (<3 biopsy cores involved) or <10-year life expectancy due to medical illness.[3] The use of active surveillance for favorable intermediate risk patients with 3+4 Gleason scores is more controversial.[4,5] For these intermediate-risk patients, contemporary methods of risk assessment and novel prognostic markers show much progress for improving risk stratification and decision-making regarding treatment vs. observation.[4] However, more progress is needed and there are still significant risks in employing active surveillance for intermediate-risk patients.[5]

Younger and healthier men or men with more aggressive cancers are generally recommended to undergo therapy with either radiation or surgery. The major side effects of radiation therapy are erectile dysfunction, in approximately 40%, and radiation proctitis. The major risks of prostate removal surgery are erectile dysfunction and stress urinary incontinence.[3] Hormone suppression therapy is most commonly used to control cancer growth after it has metastasized. Side effects from hormonal therapy include impotence, hot flashes, loss of sexual desire, breast growth or tenderness, and osteoporosis. [3]

There is no clear “right” answer for the typical patient diagnosed with prostate cancer today.[3] No clear evidence suggests one approach is significantly better than another, and the decision is often left to the treating physician and patient. Active surveillance plays an increasing role given the increased diagnosis of cancer in the post-prostate-specific-antigen (PSA) era.[3]

PSA is a glycoprotein that is expressed by both normal and neoplastic prostate tissue.[6] Most of the PSA produced by the prostate gland is carried out of the body in semen, but a very small amount escapes into the bloodstream.[7] Elevation of PSA in the blood is believed to be due a disruption of the prostate cellular structure. An elevated PSA level can occur in the setting of different prostate diseases and conditions, including prostate cancer but also as a result of non-cancerous causes.[7] Common benign causes of PSA elevation include benign prostatic hyperplasia (BPH), urinary tract infections, prostate manipulation, urinary retention, Foley catheter placement, and prostate biopsy. [6,7] Medications commonly taken to treat BPH, such as finasteride (Proscar), dustaride (Avodart), and a combination of dutasteride and tamsulosin (Jalyn) can decrease PSA by about 50% within six to 12 months of starting their use. Another medication used to treat fungal infections, ketoconazole, can also lower PSA levels. Also, herbal supplements such as saw palmetto and those containing phytoestrogens, which are plant-derived chemicals with estrogen-like effects, can lower PSA levels.[7] Other drugs that can reduce PSA levels are NSAIDs, Statins, and Thiazide group of drugs.[6]

The PSA test was originally approved by the FDA in 1986 to monitor the progression of prostate cancer in men who had already been diagnosed with the disease.[8] Beginning in 1994, some doctors and professional organizations encouraged yearly PSA screening for men 50 years of age and older. However, beginning in 2008, as more was learned about the benefits and harms of prostate cancer screening, a number of organizations began to caution against routine population screening.[8] More recently, emphasis has been placed on changes in PSA levels over time as a predictor of aggressive prostate cancer and for monitoring of patients already diagnosed with prostate cancer.[7,9] The rate of change of PSA over time is known as “PSA velocity.” [6] The usefulness of PSA velocity is in part limited by variability in serum PSA levels at different times in the same patient, irrespective of the presence or absence of cancer.[6] At least three consecutive measurements should be performed. [6] A longer time over which values are measured can help reduce the general variation, i.e., “noise”, in the PSA measurements.[6] For men with a PSA greater than 4.0 ng/mL, an average, a consistent increase of more than 0.75 ng/mL over the course of three tests is considered significant.[10]

In view of the uncertain utility of PSA as a prognostic indicator, and the side-effects of conventional treatment, men diagnosed with prostate cancer are often faced with difficult choices. The 2019 National Comprehensive Cancer Network (NCCN) Guidelines For Patients offers a detailed set of guidelines for treatment and testing for prostate cancer patients depending on graded risk factors.[11] According to the NCCN guidelines, active surveillance may be an appropriate choice for management of the disease for those with a low or favorable intermediate risk level.[11] However, due to the highly individualized nature of the decision-making in this area, men with unfavorable intermediate or higher risk levels may refuse recommended conventional treatments and instead elect active surveillance. In cases in which the patient elects active surveillance instead of conventional treatment—whether with or against medical advice--there should be alternative treatment options to assist in obtaining favorable outcomes. Systemic oxygen/ozone (O_2/O_3) treatment is a treatment option that is worthy of consideration in this regard.

It is evident that the immune system plays a primordial role in the defense of the organism against infection and cancer. Recent clinic trials have established the role of immune modulation as an antitumor strategy. Several studies by Bocci *et al*. since the 1990s clinically confirmed the action of systemic O_2/O_3 treatment as having a potential indirect antitumor effect via modulation of the immune system. The studies demonstrate that ozone can modulate the production of various cytokines, such as interleukins and interferon, and as such, modulate the activity of the immune system, which is responsible for the defense of tumor cells. Several animal preclinical studies have demonstrated that systemically introduced ozone may exercise an indirect antitumor effect via modulation of the immune system.[12] In addition, the inhibition of NFκB has been identified as an important target for the prevention and treatment of cancer.[13]

Clinical experience suggests that systemic O_2/O_3 therapy should not be used as a substitute for any other oncological treatment—never as "alternative medicine."[12] Furthermore, clinical experience suggests that systemic O_2/O_3 treatment should always be "complementary" to conventional oncological treatment, playing a supportive role. [12] In addition, patients should provide fully informed written consent, and they should receive detailed and truthful information highlighting the studies that have suggested potential usefulness of O_2/O_3 therapy, but also that data from randomized clinical trials is lacking. [12] Although O_2/O_3 therapy should not be used as a first-line treatment of cancer, what if the first-line conventional treatment consists of management by active surveillance? The patient may chose active surveillance over conventional therapies with or against oncological medical advice. But in either case, the patient deserves to be provided with options for receiving effective complementary therapy. It is the goal of this case report to demonstrate the potentially beneficial therapeutic value of O_2/O_3 treatment, applied in effective doses, for a prostate cancer patient electing disease management by active surveillance.

Case Presentation

The patient is a 64-year old male whose PSA as measured on April 10, 2018 was 9.1 ng/mL, and as measured on May 18, 2018 was 9.6 ng/mL. A needle biopsy, performed on June 25, 2018, resulted in a diagnosis of localized perineural invasive adenocarcinoma of the prostate. The tumor was found to occupy the right apex (4 mm, 15%, Gleason score 3+4=7), the left mid base (7 mm, 20%, Gleason score 3+4=7), and the left base (8.8 mm, 40%, Gleason score 4+3+7). Due to the findings in the left base, the cancer is classified within the unfavorable intermediate risk group according the NCCN guidelines.[11] As such, he would not be a candidate for disease management by active surveillance.[11] The finding of perineural invasion slightly increases the risk that the cancer has spread along the nerves outside the prostate, but does not necessarily mean that the cancer has spread outside the gland.[14]

The patient underwent hormonal therapy with Lupron for a limited time period on the recommendation of his physician. Testosterone suppression resulted in an improved PSA score, as measured on October 4, 2018, of 4.4 ng/mL. The patient thereafter chose to withdraw from the hormonal treatment. His PSA score increased to 8.7 ng/mL, as measured on November 12, 2018. In addition to rejecting further hormonal treatment, the patient also rejected other conventional treatment options, such as radiation or prostate removal surgery.

Phase 1 O_2/O_3 Treatment & PSA Results

After providing informed consent, the patient began a course of O_2/O_3 treatment. From October 15, 2018 through January 28, 2019, (phase 1), he received twice weekly O_2/O_3 treatments. One day each week, he received major auto-hemotherapy (MAH) and an ozone sauna treatment. On the other day each week, he received an ozonated saline solution (SSO3) treatment and an ozone sauna treatment. The two weekly treatments were usually spaced 2-3 days apart.

The MAH treatments were provided using the Ozonette ozone generator, manufactured in Spain by SEDECAL; he received a concentration of 50 µg/mL and a volume of 100 mL. The SSO3 treatments were provided using Medazons-BM ozone generator, manufactured in Russia by Medazons, at a marked concentration of 2500 µg/L (2.5 µg/mL); the volume of saline solution was 200 mL, which was saturated for 10 min before beginning the I.V. transfusion. The ozone sauna treatments were provided using the EXT120, manufactured in Canada by Longevity, and a Longevity sauna; the concentration used was 20 µg/mL at a rate of 1/8 L/min, for 20 min, at a temperature of 40-41°C. All ozone generators were used with medical grade oxygen.

The PSA score measured early in phase 1 on November 12, 2018, as already mentioned previously, was 8.7 ng/mL. The PSA score measured at the end of phase 1 on January 29, 2019, was 9.7 ng/mL. This was similar to the 9.6 ng/mL score that was measured on May 18, 2018, before the patient began hormonal treatment.

Phase 2 O_2/O_3 Treatment & PSA Results

This phase occupied the time period from February 1, 2019 through June 4, 2019. During this phase, the treatments were irregular due to the patient's personal circumstances. From February 1, 2019 through March 25, 2019, the patient received twice weekly treatments of MAH and ozone sauna, as described above. There was a break, and treatments resumed with once per week MAH treatments, as described above, from April 17, 2019 through June 3, 2019. The PSA score, measured on June 4, 2019, was 12.4 ng/mL.

Phase 3 Treatment and PSA Results

This phase occupied the time period from June 12, 2019 through August 28, 2019. During this phase, the patient was able to come once per week. He received once per week MAH and ozone sauna treatments, as described above, each treatment day. The PSA score, measured on September 4, 2019, was 14.7 ng/mL.

Phase 4 Treatment and PSA Results

This phase occupied the time period from October 14, 2019 through December 2, 2019. After a break, the patient resumed O_2/O_3 treatments on October 14, 2019. He received twice weekly treatments from October 14, 2019 through December 2, 2019. One day per week, he received SSO3 treatment, as described above. However, on the other day each week he received MAH treatment using a lower concentration of 30 µg/mL, along with ultraviolet blood irradiation (UBI) therapy. The two weekly treatments were usually spaced 2-3 days apart. The PSA score, measured on December 4, 2019, was 11.7 ng/mL.

Discussion

Analysis of the PSA Results During Phases 1-4

At the end of phase 1, the patient returned to his pre-hormonal- treatment PSA level. This could be related to a normalization of testosterone to its pre-hormonal-treatment levels. However, the phases 2 and 3 PSA results show a five-point increase in the PSA score. This was followed by a three-point improvement following the phase 4 treatment. Ultimately, the causation of the fluctuation in PSA results in phases 1- 4 may be difficult to ascertain due to several unknown or unaccounted for variables in the patient's overall health picture that are known to affect immunity and PSA levels. These variables include stress, diet, supplements and vitamin therapy, and possible hormonal fluctuations. One known variable that occurred during phase 4 was the introduction of the UBI therapy. Another major unknown variable consists of the rate at which the PSA would have changed in the absence of the O_2/O_3 treatment.

Nonetheless, the three-point decrease in PSA after phase 4, following a five-point increase in phases 3 and 4, was noteworthy. These are significant fluctuations that occurred in relatively short time periods. Despite the variables involved, the PSA increase during phases 2 and 3 could be related either to the concentrations and dosages used or to the irregularity of the treatment regimen during these phases. It seems significant that a lower dosage and a regular treatment regimen was observed in phase 4, which could account for the improved PSA score. It is reasonable to conclude that even relatively small changes in concentration, dosage and frequency of treatment could have made a significant difference in the treatment outcome in this case.

Dose Dependent Effects of O_2/O_3 Therapy

This effectiveness of O_2/O_3 therapy depends on the concentrations and dosages that are used. In clinical practice, when systemic O_2/O_3 therapy is performed the ozone does not enter into the blood circulation and has no direct effect on cancer cells.[12] Its effects are indirect and are mediated by secondary messengers that induce a further adaptive response from the body. 4-hydroxynonenal (4-HNE) and H_2O_2 are among the most relevant secondary messengers induced by ozone during lung toxicity following airway inhalation, but also in the course of the induction of beneficial effects during medical application.[12] H_2O_2 can enter the cytoplasm of mononuclear cells, activate tyrosine kinase, and phosphorylate the transcription factor NF-kB, which can act as regulator of signal transduction and, as such, represents a crucial mediator of those defense and immune responses. The important role of the transcription factor nuclear factor erythroid-derived 2 (Nrf2) induction by ozone in order to enhance the antioxidant systems has been described. [12]

The indirect effects O_2/O_3 therapy occur in a hormetic dose-response relationship. [12] "Hormesis" means "the beneficial effect of a low level exposure to an agent that is harmful at high levels." [15] Ozone concentrations and effects do not follow a linear relationship: very low concentrations may have no effect and very high concentrations can lead to contrary effects to those produced by lower/middle concentrations. [12] Concentrations in the range of 20 to 80 µg/mL are considered to be therapeutic. [15] However, there are varying therapeutic effects within that range.

The Madrid Declaration on Ozone (2nd ed. 2015), adopted by the International Scientific Committee on Ozone Therapy (ISCO3), sets forth non- binding guidelines for the clinical use of ozone therapy based on scientific research in different countries and many years of experiential and clinical practice.[16] In the Madrid Declaration, the ISCO3 recommends the use of low doses of systemic ozone treatment when the intended effect is to have an immunomodulatory effect. A low dose of MAH, for example, would utilize a concentration of 10-20 µg/NmL, and a volume of 50-100 mL depending on the patient's weight, yielding a dose in the range of 0.5 to 2.0 mg. Medium doses, using MAH concentrations of 20-30 µg/NmL, are immunomodulatory and stimulate the antioxidant defense. High doses, using MAH concentrations of 30-40 µg/NmL, have an inhibitory effect on the mechanisms that occur in autoimmune diseases. [16]

The lower ozone concentration used in the fourth phase in this case may have been more effective for modulation of the patient's immune system than the higher concentrations and doses used in the first three phases.

Conclusion

When used in effective concentrations and dosages, systemic O_2/O_3 treatment can potentially be used as a complementary therapy for prostate cancer patients electing disease management by active surveillance. Further study is warranted.

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