

Case Report

Treatment of androgen-refractory prostate cancer with UV light blood-irradiation: A case report

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Accepted 29 October, 2010

UV blood-irradiation (UBI) using the ImmunoModulator (IM) is in clinical studies for treatment of patients infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Preclinical studies suggest UBI could be also effective against cancer. To further explore this potential, a patient with an aggressive prostate cancer that has recently become androgen-refractory was treated with UBI using the IM. Cancer progression was monitored by means of prostate specific antigen (PSA). Prior to treatment with UBI PSA level increased exponentially over 6 months with a doubling time of 2.3 months. After treatment PSA level increased at a slower rate of 4.0 months doubling time. It is concluded that UBI treatment using the IM has an inhibitory effect on the growth of prostate cancer, presumably by stimulating a cellular immune response. Since androgen-refractory prostate cancer is invariably fatal, clinical studies with the IM are warranted for this indication.

Keywords: Androgen-refractory prostate cancer, immune response, prostate specific antigen, UV blood-irradiation, ImmunoModulator.

INTRODUCTION

In the early 20th century, the search for a cure for infectious diseases led researchers in many directions, one of which was UV light blood-irradiation (UBI). During the 1930s the Knott portable UV blood irradiator was used in treating infectious bacterial and viral diseases in thousands of patients (Knott, 1948). By the mid 1940s, the machine's use was well documented, e.g. for the treatment of viral hepatitis (Olney, 1955). These and other studies (see Rowen, 1996 for review) demonstrated the safety of UBI and described improvement in patients' condition. However, no controlled studies demonstrated efficacy.

Reduced interest in this therapy coincided with the advent of antibiotic therapy for bacterial infections and vaccines against many viral infections. In addition, the lack of scientific explanation for the efficacy of UBI placed it at the fringes of medical practice.

In recent years, the spread of chronic viral diseases such as AIDS and viral hepatitis sparked renewed interest in UBI. The medical device company Energex Systems, Inc. (Allendale, NJ) developed a modified

device for this purpose, the ImmunoModulator (IM). A significant improvement over the Knott machine is the use of a more efficient medium pressure mercury lamp as a light source, emitting a broad-band of UV light (200-400 nm). This lamp contains 1000-fold less mercury and uses air rather than circulated water for cooling. This results in a smaller machine that is easier to operate (Ben-Hur et al, 2005). Following preclinical studies of the IM (Ben-Hur et al, 2004) it entered clinical studies for HCV and AIDS patients, both of which responded favorably during Phase I (data under review at the FDA).

UBI appears to exert its effect by modulating the immune response of the patient, hence the name of the device, IM. The immune system is important in controlling cancer, most likely via NK cells of its cellular arm (Moretta L, 2007), leading to its application for cancer therapy (Armstrong et al, 2001). Preclinical studies demonstrated a significant reduction in the rate of tumor growth in mice implanted with breast cancer after treatment with the IM (Dr. K. Kousoulas, Louisiana State University, Baton Rouge, LA, personal communication).

In humans, androgen-refractory prostate cancer presents a unique opportunity for a clinical evaluation of the effect of UBI on cancer progression. This is because in patients that have undergone prostate ablation by

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Figure 1. Treatment with the IM.

either surgery or irradiation in conjunction with primary hormonal therapy, prostate specific antigen (PSA) is below the level of detection. If cancer cells spread beyond the prostate capsule at the time of treatment onset, the patients become eventually androgen-refractory as defined by renewed PSA progression (Heidenreich, 2005). The rate of PSA doubling time is about 2 months in the case of aggressive prostate cancer (high Gleason score). PSA thus serves as an indicator for the rate of cancer growth in such patients and the effect of treatment can be monitored by PSA level. Although a number of treatment options exist at this stage, the disease is invariably fatal and additional treatments are urgently needed.

In this paper, we report on a case of androgen-refractory prostate cancer patient treated with the IM. This patient was deemed an attractive candidate for treatment because of the exponential increase of his PSA at the early stage of the androgen-refractory state. By monitoring PSA level a significant response to UBI treatment was observed, i.e. a 1.8-fold reduction in the

rate of PSA level increase over time.

SUBJECT AND METHODS

A 65 years old white male was presented with highly elevated PSA (270 ng/ml) and enlarged prostate. Upon biopsy an aggressive prostate cancer was diagnosed (Gleason score 8-9). Hormonal therapy was initiated using Lupron depot (leuprolide acetate, 30 mg every 4 months) followed 2 months later by intensity modulated external beam radiation therapy, 5 times per week, over the course of 9 weeks. PSA levels gradually declined during treatment. By 11 months after therapy commenced, PSA was undetectable (<0.1 ng/ml) and the prostate gland shrank from 60 to 12 ml. Hormonal therapy was continued and PSA level monitored at 4 months intervals. About 4 years after diagnosis, PSA level started to increase at an exponential rate, indicating conversion to an androgen-refractory state.

About 6 months after onset of the androgen refractory state the patient opted for treatment with the IM, prior to starting secondary hormonal treatment with Casodex (bicalutamide 50 mg tablets). IM treatment (Figure 1) was carried out in the doctor's office and consisted of drawing 200 ml venous blood into a reservoir. The blood was then passed through a flow cell in the device at a

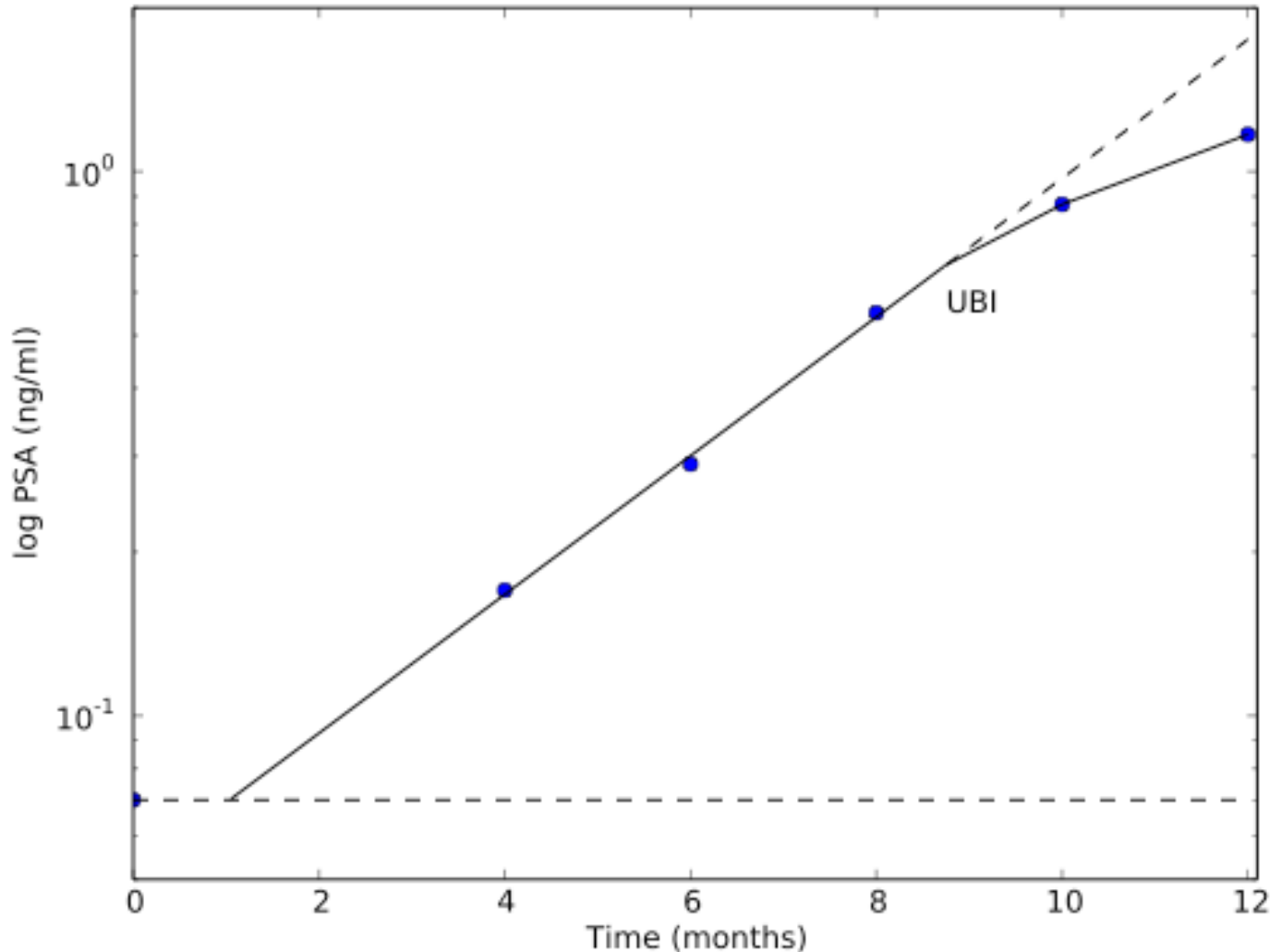


Figure 2. PSA levels at 2 months intervals. Note that PSA is on a \log_{10} scale. The time of UBI treatment is indicated. The dashed lines denote the expected PSA increase in the absence of treatment and the base line level.

constant flow rate for 8 min. During the transit of the blood in the cell (29 sec) it was exposed to broad-band UV light (200-400 nm) at an irradiance of $5\text{mW}/\text{cm}^2$ (254 nm) and was then returned to the patient's vein. The whole process lasted about 30 min. Vital signs were monitored before, during and after the treatment. No change was observed in blood pressure, body temperature and heart rate. There were no adverse effects as a result of the treatment. The patient signed an informed consent form prior to treatment. The initial treatment was repeated twice more, one and three days after it has begun.

RESULTS

Figure 2 shows that after conversion to an androgen-refractory state PSA increased exponentially. From the slope it was calculated that the doubling time was 2.3 months, the typical range observed for such an aggressive prostate cancer. After the patient was treated

with the IM, subsequent increase of PSA was at a slower rate (Figure 2). Note that there are two data points after treatment and that the break occurred immediately after treatment. From the slope of the curve it was calculated that doubling time of PSA during the 3 months follow up was 4.0 months. Our studies with HCV patients indicated that the response to the IM treatment lasts about 3 months. The patient opted at this time to start secondary hormonal therapy with Casodex. This caused a reduction in the PSA level from 1.2 to 0.4 at 2 months after the start of Casodex. A second course of IM treatment was implemented at this time. PSA level dropped further to 0.3 at 2 months after the IM treatment. It should be noted that because of the early stage of the disease the patient displayed no symptoms either before or after treatment with UBI. Also, imaging using MRI or bone scanning was negative at this stage. PSA was therefore the only indicator for disease progression and treatment outcome.

DISCUSSION

The results presented in this paper clearly demonstrate a marked response of an androgen-refractory prostate cancer patient to a treatment with UBI using the IM device. This response was reflected in a reduction of 1.8 fold in the rate of increase of PSA during 3 months follow up after treatment. This is only a rough estimate as there were only two data points after treatment. However, because of the very predictable PSA increase, the change in rate is unambiguous. Further support for the effect of UBI comes from the second IM treatment after the patient started on Casodex. In this case PSA went down from 0.4 to 0.3. Although this effect was less clear-cut, it is consistent with the effect of the first IM treatment.

While encouraging, this case study leaves quite a few open questions. First, what is the duration of the effect of a single treatment. Second, would additional treatments have the same effect. Third, would the response to additional treatments stay the same over time. Fourth, would the slower rate of PSA increase be reflected in a longer life-expectancy for the patient. Fifth, what is the mechanism of action of IM treatment. Presumably, these effects are due to a stimulation of the cellular immune system, but the mechanism of stimulation is not known at this time. Previously we suggested (Ben-Hur et al, 2005) that exposure to UV light induces production of immune modulators (interleukins) by leukocytes exposed to UV light. The interleukins then mediate the immune response to cancer and pathogens. Indeed, treatment of rhesus monkeys with IM induced the expression of a variety of genes involved with immune response, measured using DNA arrays (Dr. P. Marx, Toulane University, LA, personal communication). The ability of UV light to induce gene activity is well established (Brenneisen et al, 2002, Tyrrell RM, 2004, Van Laetham et al, 2009) and the genes that are activated depend mostly on the target cells. Unfortunately, little or no work has been done on leukocytes in this respect. Red blood cells are also affected by UBI (Zalskaya et al, 2009). This effect is reflected in photodissociation of hemoglobin (Hb), converting HbO₂ to deoxyHb with a concomitant increase in pO₂ in the treated blood. However, since only about 4% of the patient's blood is treated at a time, this is of no clinical significance.

In conclusion, the ability of UBI treatment to slow the progression of prostate cancer in an androgen-refractory patient is clinically important and deserves further clinical studies to establish the role of this treatment in the management of such patients.

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