British Journal of Medicine & Medical Research
17(5): 1-6, 2016, Article no.BJMMR.27895
ISSN: 2231-0614, NLM ID: 101570965

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Stabilization of Prostate Cancer with *Amanita phalloides*: Intervals with 5-Alpha-Reductase Inhibitors and Melatonin to Circumvent Resistance: Case Report

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/27895
Editor(s):
(1) Arun Kumar Nalla, College of Medicine, University of Illinois, Peoria, IL, USA.
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Complete Peer review History: http://www.sciencedomain.org/review-history/15820

Case Report

Received 24th June 2016
Accepted 2nd August 2016
Published 17th August 2016

ABSTRACT

Aims: Amanita phalloides contains alpha-amanitin, inhibiting RNApolymeraseII. Due to overexpression of switch genes in tumor cells, RNApolymeraseII is used to full extent there. Partial inhibition with amanitin influences tumor cell - but not normal cell - activity. A patient with diagnosed prostate cancer was treated successfully for six years with Amanita alone, prostate specific antigen levels increased slowly. However, the necessary dose for stabilization of the level increased during this time. To circumvent further habituation or resistance, other therapeutics were applied in intervals.

Presentation of Case: Inhibitors of 5-alpha-reductase were applied in intervals of pausing Amanita. They can further stabilize the prostate antigen level, but tumor cells became resistant to this drug after a few months. The patient suffered under severe side effects. Melatonin was applied in one interval together with Amanita. It shows no additional side effect, but no additional advantage for the patient occurs.

Discussion and Conclusion: Amanita is the drug for long term stabilization of a tumor patient. Fast occurrence of resistance was never observed so far. 5-alpha-reductase inhibitors can be

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applied in shorter intervals, with speedy development of resistance. Melatonin has no advantageous effect for this patient. Consequent monitoring for all therapy steps is recommended.

Keywords: Amanita phalloides; prostate CA; tumor therapy; 5-alpha-reductase inhibitor; melatonin.

1. INTRODUCTION

A tumor can develop in any tissue, as well the prostate can be affected. Different kinds of growth activity and metastasising activity occur, dependent of the origin of proliferation. A slow growing benign prostate cancer can remain silent, an aggressive malignant tumor may cause difficulty in urinating, problems with sexual intercourse, including erectile dysfunction and pain. Prostate cancer tends to develop in men over the age of 50, it is one of the most prevalent type of cancer in men. Diagnosis may be indicated by symptoms, physical examination, prostate specific antigen (PSA), or biopsy.

In studies with tumor forming Drosophila melanogaster, four classes of genes involved in tumor formation could be distinguished. Proliferative genes break the cell cycle control by allowing replication immediately after mitosis. One single proliferative mutation is sufficient for tumor formation [1]. Mutations in oncogenes and tumor-suppressor genes are secondary events and add by destabilization of the differentiation pattern of the cells. In search for ubiquitous events - the central possible targets for therapeutic intervention - switch genes were identified. All switch genes belong to the class of HOX genes, and code for RNApolymeraseII (RNAP) transcription factors. Some HOX genes are overexpressed in human tumor cells [2]. Due to this overexpression, the event that leads to tumor cell growth should lead to high activity of RNAP. In somatic cells of adults, RNAP is expected to be less active. Partial inhibition of this enzyme consequently causes inhibition of tumor cell activity, without effects on somatic cells. The drug in the extract of Amanita phalloides, alpha-amanitin, blocks RNAP in all cells. Inhibition of about 50% of this molecule breaks tumor cell activity. The immune system then recognizes and destroys tumor cells.

5-alpha-reductase catalyzes the conversion from testosterone to dihydrotestosterone. The latter is responsible for normal and hyperplasic growth of prostate cells. The genetically transmitted disease of 5-alpha-reductase deficiency leads to a very small prostate size throughout life. Consequently, since the 1990th 5-alpha-reductase inhibitors like Finasteride were used to treat prostate hyperplasia, with a castration like effect [3,4]. In a new study it shows, that Finasteride could reduce the PSA level by approximately 40 % during therapy, however in those cases the volume of the prostate hyperplasia was not affected and did not correlate with the PSA [5]. There is an overall link between prostate cancer and PSA serum levels. PSA levels increase as well during inflammations. Finasteride may as well reduce inflammation-associated PSA elevation [6]. Basically there is no difference between different 5-alpha-reductase inhibitors [7].

Melatonin, produced during the night in the pineal gland, convey information concerning the circadian rhythm to body structures. Circadian rhythms are core regulators of mammalian physiological processes. The production is synchronized by light, a disturbed secretion increases the predisposition for diseases. A wide range of cells exhibit melatonin receptors, reflecting the wide variety of effects [8]. In a model system for rat mammary carcinoma augmented effects by melatonin in addition to probiotic and prebiotic treatments are found. Melatonin amplifies prodifferentiating, antiproliferative and immunemodulatory activites [9]. Dysregulation of the synthesis activates cellular stressors and locally may allow neoplasic growth. Altered DNA repair could as well support tumor growth [10]. Melatonin shows pleiotropic anti cancer effects *in vitro*. Oncostatic and antiproliferative action is described, induction of apoptosis and inhibition of invasion is discussed. Together with the immunemodulating effects this drug could be effective in cancer treatment [11].

Here a long term pilot study of treatment of a patient with prostate cancer is described. Long term basis is treatment with Amanita phalloides, interrupted later for treatment intervals with 5-alpha-reductase inhibitors, and an interval with additional melatonin administration.

2. PRESENTATION OF CASE

The patient was born in March 1936. His mother died with a stomach carcinoma at the age of 91.

No other predisposition for tumor formation was identified.

In 1991 intestinal polyps (adenoma) were removed. In 1997 a cyst (adenoma) of the left kidney was removed. In 1999 two additional adenomas were removed. In 2002 an additional adenoma was removed. The physical examination of the prostate in 2003 lead to a normal finding, a suspect finding appeared in 2004. In July 2004 prostate cancer was diagnosed by biopsy. 18 out of 36 tissue samples showed an infiltration with tumor cells, with a Gleason score of 3+4. Tumor cells are hormone dependent. At that time the serum PSA level was at 7,4 ng/ml. No operation and no radiation took place. From August 2004 on Enantone, Methotrexat and Leuporelinacetate were applied, the PSA dropped to 0,1 ng/ml. From 2006 to 2008 treatment with different hormone inhibitors occurred**.** In 2006 two additional adenomas were removed. In 2006 two benign verucca were removed. The patient decided beginning of 2008 to stop all hormone blocking treatments. PSA at that time increased from 0,1 to 0,8 ng/ml.

Amanita therapy is administrated with Amanita phalloides (zert. Riede) dilutions [herbamed AG]. Amanita phalloides dilutions are applied since 300 years, the classical homoeopathic indication is fear of death. With 100 ml of Amanita phalloides (zert. Riede) D2, about 50 % of all RNAP molecules in all cells are inhibited. Degradation of the drug cannot be named. With different doses the patient is usually stabilized for years.

Body weight is around 110 kg, was stable during Amanita therapy and increased during 5-alpha-reductase inhibition. In addition to Amanita, the oral uptake of essential fatty acids and dermal application of Zinc salve is indicated. Essential fatty acids enhance the fluidity of cellular membranes, and decrease the risk of autoimmunity [12].

For monitoring of the therapy, the regular measurement of following parameters is arranged: PSA and Lactatedehydrogenase (LDH) in serum. LDH is present in every cell, the occurrence in serum shows degradation of cells. LDH levels increase in all events resulting in cell degradation, i.e. myocardial or kidney infarction, embolism, autoimmunity, anemia, infectious diseases – or digestion of tumor cells. PSA levels are population specific and age associated [13]. Long term therapy should consider a certain increase during time. The expected increase during ageing between 70 and 80 would be 35 % (Fig. 1) [14]. The objective of a long therapy therefore was to keep the PSA level low with always the minimum dose of the drug.

Amanita therapy starts in November 2008 (Fig. 1). With a dose of 1 ml of Amanita phalloides (zert. Riede) D2. An initial level of amanitin is reached in February 2009 that inhibits about 50 % of all RNAP molecules. Further treatment occurred with 5 drops of Amanita D4 daily until November 2011, followed by a dose of 15 drops of D3 daily until June 2010. Amanita D2 was administered from that time on with different doses. In October 2013 a basaliome was excised (CM D0). In December a colonoscopy remained without diagnostic finding. In June 2014 the patient decides to interrupt the Amanita therapy. Immediately PSA levels rise with a rate similar to that in 2008, when anti hormone treatment was interrupted. In addition he suffered from a tick bite, without an erythema migrans. A preventive treatment with 100 ml Terebinthina laricina D1 in 2 x 15 drops per day occured. Terebinthina laricina inhibits Borrelia infections. A possible Borrelia infection can support tumor growth of cells [15].

Initially 50 ml of Amanita phalloides D2 were taken per year in 2010, in 2015 a dose of 50 ml is necessary per month to further stabilize the PSA level. Habituation of the cells is observed. Therefore the strategy of therapy changed in January 2015. Intervals of different therapies occurred (Fig. 2). Resistance to Amanita should be reduced during an interval with another medicine. First 5-alpha-reductase inhibitor (Finasteride 5mg daily) was applied. PSA level could be stabilized until May 2015, then rised again. The patient suffered during this interval from fatigue, listlessness and increase in weight. A changeover to Dutasteride (0,5 mg daily) brought no advantage.

In June 2015 the Amanita interval started with a dosage of 4 x 10 drops of D2 daily, correlating with an uptake of 50 ml monthly. Immediately the LDH level increases. This shows cell destruction, it can be concluded that Amanita induced it. PSA level increases as well. This elevation is frequently observed in cases, where cells are disrupted and set their intracellular PSA free [16].

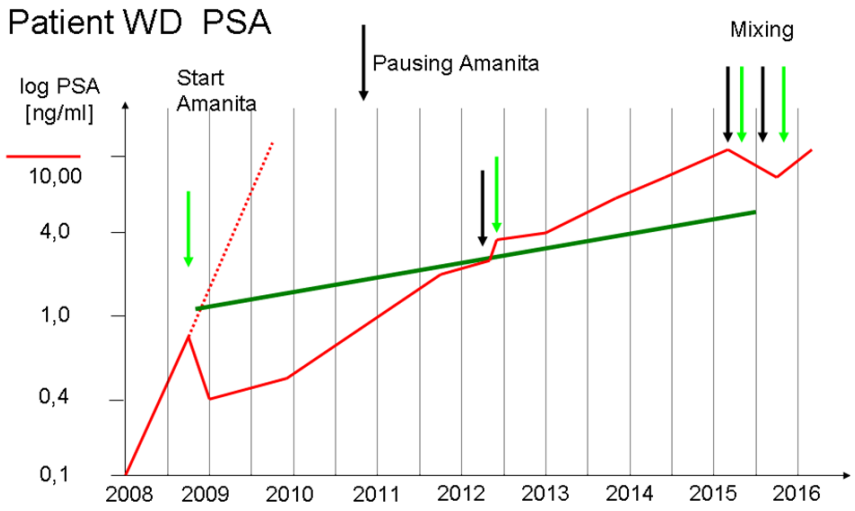

Fig. 1. Amanita therapy

Shown is the PSA level (red line) during the Amanita therapy beginning in 2008 (green arrow). The dotted red line shows the elongation of the increase of PSA during the time without any tumor specific therapy. In 2008 a dose of 1 ml Amanita phalloides D2 was administered daily. Immediately, the PSA level decreased. With variable doses further stabilization was possible. In April 2012 the patient decided to interrupt the Amanita therapy (black arrow). PSA levels increased with a similar rise than in the untreated phase in 2008. After that period, further treatment occurs with Amanita alone until the beginning of 2015. Shown is as well the expected age specific increase of PSA (green line)

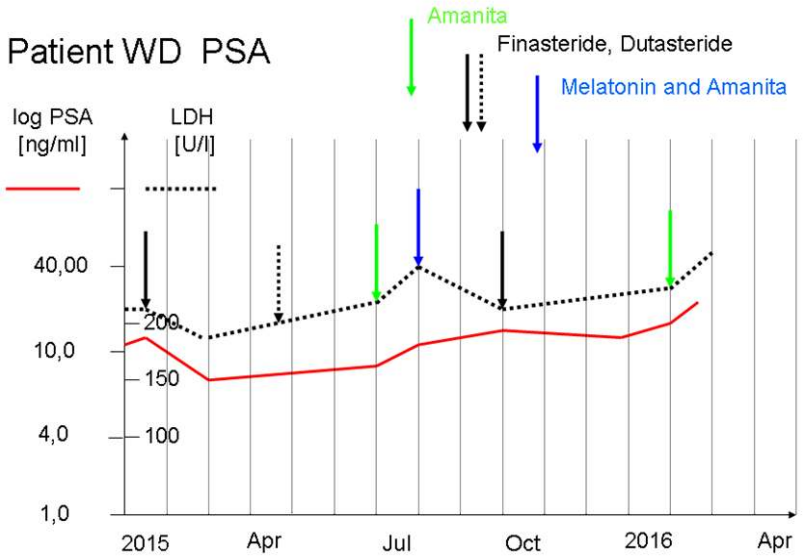

Fig. 2. Interval therapies

Amanita phalloides (green arrows) and Finasteride, Dutasteride (black arrows) therapy intervals were applied. In addition to Amanita Melatonin (blue arrow) was administered for two months in August and September 2015. PSA (red line) and LDH (black dotted line) levels are outlined

In August and September 2015 in addition to Amanita, melatonin (20 mg daily) was applied. Within this period, LDH decreases and PSA increases. In this case, additional tumor growth instead of tumor reduction is expected. Therefore, melatonin does not amplify the effect of Amanita but destroys it. As there was no advantage for the patient, melatonin administration stopped and was not repeated.

Another period of 5-alpha-reductase inhibition started in September 2015. It ended four months later, when again a PSA increase occurred. Since then the patient is treated with Amanita phalloides D2 alone, with good results in stabilization so far. Further intervals with 5-alpha reductase inhibition will follow. Other options for therapies are not yet indicated.

3. DISCUSSION

In many cases, Amanita phalloides inhibited tumor growth for years. The patients stay at life in life without complications or severe side effects that would influence quality of life. No hospitalization is necessary. The drug is stable at room temperature and can easily be applied everywhere where the patient stays.

Amanita usually breaks the activity of specifically tumor cells, without affecting somatic cells. The immune system remains intact and is able to recognize and digest tumor cells. However, the Amanita dose necessary for stabilization increases over the years. To break this tendency, intervals with other therapies are applied. Another selective pressure to the cells should let grow out resistant cells.

5-alpha reductase is the necessary enzyme for dihydrotestosterone synthesis, which is required for prostate cell proliferation. Inhibitors of this enzyme are used in therapy of prostate hyperplasia, and can be used here to avoid PSA increase for four to five months. After these intervals, the Amanita effect can be achieved immediately: increase of LDH, reflecting cell degradation of presumably tumor cells.

Melatonin showed anti tumor activity in *in vitro* tests. However, in this patient no anti tumor effect could be found: PSA level increased during the application of melatonin. And the cellular degradation, induced by Amanita, reflected in higher LDH levels, was eroded.

4. CONCLUSION

Each tumor specific therapy should be applied alone, with a minimal dose, for a maximal duration. Frequent laboratory tests are necessary to optimize their application. With this strategy, other therapy options, like the use of Chelidonium majus, or X-ray, or chemotherapy, still are open.

The patient presented here had no side effects originating from the Amanita therapy. Until today he showed no clinical symptom of a prostate hyperplasia, nor any signs of complications. This high quality of life reflects the goal of a good tumor therapy.

CONSENT

The author declares that 'written informed consent was obtained from the patient for publication of this paper and accompanying images'.

ETHICAL APPROVAL

Only existing drugs in usual doses are used during this study. No new drug was applied. Therefore no ethical permission is necessary in this case.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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