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PERSONALIZED TREATMENT OPTIONS REPORT

PREPARED ESPECIALLY FOR
DR. XXXXX X. XXXXX

PREPARED BY
MOSHE ROGOSNITZKY
ADJUVANT MEDICAL SOLUTIONS
WWW.ADJUVANTMED.COM

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INTRODUCTION

Dr. Xxxxx was diagnosed with prostate cancer in December 2000. Initially he opted for watchful waiting in addition to lifestyle changes and alternative medical approaches. In May 2004 an MRI scan showed lymphadenopathy and hormonal therapy was started. Whilst the hormonal therapy has consistently lowered the PSA (which was unusually high with very extreme fluctuations), disease progress has continued. Furthermore, Dr. Xxxxx has suffered a number of episodes of DVT since beginning hormonal therapy. He has required constant anticoagulation therapy with low molecular weight heparin which has only partially resolved the DVT symptoms.

Dr. Xxxxx has therefore been seeking a new treatment approach which is comprehensive in that it takes into account his primary disease as well as co-morbidities and seeks to correct the cellular abnormalities, nutritional deficiencies and toxicological accumulations which may be impacting his disease process.

What follows is an overview of his diagnostic situation and a selection of those options deemed to be most appropriate in this situation together with the rationale for each. These are chosen primarily for their favorable risk-benefit ratio as well as their ability to simultaneously target the comorbidities involved. Modifications should be made based on ability to comply with regimen and response. Any decision on implementation of all or part of the options below should be made by Dr. Xxxxx's physicians.

DIAGNOSTIC OVERVIEW

HISTORICAL FINDINGS

Diagnosed with prostate cancer Gleason 3/3 in December 2000. Gradual adenopathy beginning on April 2004. Adenopathy has since spread from groin to abdomen and neck. Largest abdominal lymph nodes measure 26mm and groin lymph nodes measure 24mm in both groins. Left sided hydronephrosis is present due to lymphatic obstruction of the ureter. Inability to urinate due to a damage caused by a manual prostate examination in 2004 necessitating daily self-catheterization.

PSA fluctuations from <3 to >1000, often these fluctuations are very rapid and seem to be influenced by infections.

Extensive left arm DVT and suspected left leg DVT in May - August 2006. Recurring episodes of left leg DVT-like symptoms since. Recurring episodes of penoscrotal oedema. Occasional episodes of urinary tract infections.

Liver failure in March 2006 due to hormonal therapy. Resolved spontaneously after stopping Casodex.

Most recently, an episode of cellulitis and pneumonia with sepsis. Treated in hospital with antibiotics.

Impotency since beginning hormonal therapy. General weakness, recurrent episodes of insomnia, lethargy, pain in left leg, ribs, liver area, feeling of “heaviness” in legs, inability to concentrate well. Poor sleep quality. Chronic mild anemia.

Weight 207lbs (94k.g.) Blood Pressure 130/70

LABORATORY FINDINGS

Results in black = positive findings
Results in red = negative findings

General

↓ HgB 11g/dL (RBC 3.57)
↓ Serum Iron (9umol/L)
↓ Iron Saturation 18%
↑ Fibrinogen 3.5 g/L
↑ Plasma Homocysteine 9.10 umol/L
Caeruloplasmin 0.46g/L
↑ Copper (serum) 28 umol/L (ref 10.9 – 23.5)
↑ Total IgE 172 kIU/l (ref <100)
↑↑ PSA >1000 ug/l
↑ Serum creatinine (111 umol/L)

Urinary Organic Acids

↑ β-Hydroxyisovalerate 28mcg/mg creatinine (ref <11)
↑ Methylmalonate 5.1mcg/mg creatinine (ref <4.8)
↑ 5-Hydroxyindoleacetate 8.3mcg/mg creatinine (ref 1.5 – 7.6)
↑ Pyroglutamate 16.7 mcg/mg creatinine (ref <16)
↑ Phenylpropionate 0.40 mcg/mg creatinine (ref <0.07)
↑ p-Hydroxyhenylacetate 49 mcg/ml creatinine (ref <45)

Clotting Factors

↓ Antithrombin III activity (0.69 IU/ml ref 0.80 – 1.50)
↓ Protein S Clotting Assay (0.13 IU/ml ref 0.70 – 1.80)
MTHR gene mutation positive (heterozygous) for c677T mutation

Platelet Aggregation Studies

↑ Collagen/ADP (54 secs ref 65 – 105)
↑ Collagen/Epinephrine (69 secs ref 79-164)

Toxicological Findings

↑ Lindane (2.2ug/l ref <0.9)
↑ Polybrominated biphenyls (PBBs) (1.15ug/l ref <0.5)
↑ Simethyl phthalate (1.9ug/l – above average)

DNA Adducts

Lindane 12ng/ml on SOD1 gene-chromosone 21
Copper complex 18ng/ml on chromosones 6 & 8
Arachidonate-related chemicals 10ng/ml on GSH-PX gene (q8)

Lymphocyte sensitivity tests

↑ Lindane (335 linear units ref <200)

Superoxide Dismutase Studies

↓ Zn/Cu-SOD (181u ref 240-410)
↓ EC-SOD (24u ref 28-70)

Fatty Acid Analysis

↓ GLA ω-6
↓ DGLA ω-6
↓ EPA ω-3
↓ DHA ω-3

Cytokines & Growth Factors

↑↑ IL-2 gene expression
↓ Interferon-α gene expression
↑↑ Survivin gene expression
↓↓ Dextrorotatory Lactic Acid level
↑↑ IL-6 Gene Expression
↑↑ MMP-9 gene expression
VEGF gene expression – not detectable
↑↑ Non-genomic DNA/RNA levels
↑ anti-p53 antibodies (mutated)
↑↑ TM-2PK
↑ IL-8 gene expression
↓↓ IL-10 gene expression
↓↓ TNF-α Gene Expression
↑ Telomerase
↑↑ CD10 gene expression
↓↓ IL-4 gene expression
↑↑ IL-5 gene expression
↑↑ CD10 gene expression
↑↑ IL-12 gene expression
↑↑ Interferon-γ gene expression
↑ TGF-β gene expression
↓↓ BCL-2 gene expression
↓↓ MMP-2 gene expression
↑↑ TNF-β gene expression
↓ p-185 (HER-2) level
↑↑ p21 gene expression

Neurotransmitters

Adrenaline- Trace
Noradrenaline – Trace
Dopamine - Trace
5-HT – Trace
GABA – Trace
Acethycholine – Trace

Neurotransmitter Metabolites

Adrenaline Metabolites - Absent
Dopamine Metabolites – Absent
Noradrenaline Metabolites – DOPEG - Increased
Normetanephrine - Absent
MOPEG - Absent
Serotonin Metabolites - Trace

Neurotransmitter Precursors

DOPA – Absent
Phenylalanine – Absent
Tyrosine – Absent
5-HTP – Absent
Tryptophan – Normal

Neurotoxins and False Neurotransmitters

↑ Dihydrophenylpropionic acid (acts as DA)
↑ Indole-3-propionic acid (acts as 5-HT)
↑↑ N-Methyl-R-Salsolinol
↑ Phthalates
↑↑ Tartaric acid
↑ THP

Neuropeptides

↑↑↑ Angiotensin II
↑↑↑ Bradykinin
↑ Met-Enkephalin

Hormonal Findings (urinary)

Testosterone – Trace
Dihydrotestosterone (DHT) – Trace
DHEA – Trace
↑↑↑ Beta-Estradiol

Metabolic Stool Analysis

Beta-glucuronidase (undetectable)
↓↓ Bile acid – lithocholic acid
↓↓ Bile acid – deoxycholic acid

Microbiology Stool Analysis

Lactobacillus species (undetectable)
↓ Bifidobacterium
↑↑ Citrobacter-freundii
↑ Rhodotorula species
↑ Saccharomyces cerevisiae

Food Allergy (IgE/IgA Reactions)

Broccoli – low response
Brussels sprouts – low response
Cabbage – low response
Potato – low response
Pork – low response
E210 benzoate – low response

SUMMARY OF FINDINGS

The apoptotic process is at best only partially active. p53 is mutated and probably dysfunctional, evidenced by the up-regulation of p21 as an alternative apoptotic pathway. However, any pro-apoptotic action is hampered by very high levels of the anti-apoptotic survivin. Glycolysis is very active, contributing to tumor growth. Inflammation is very active evidenced by extreme elevation of IL-6 and bradykinin. Bradykinin is also involved in proliferation of prostate cancer. It probably also contributes to the pain being experienced.

Angiotensin II is extremely elevated. This is a known growth factor for cancer, and prostate cancer in particular[1-3], via interaction with the Angiotensin II receptors which are particularly abundant in the prostate. In order to prevent treatment failure when targeting the Angiotensin II receptors, such therapy must be combined with suppression of bradykinin[4,5].

Whilst testosterone is being adequately suppressed as per the intended clinical aims, this is not leading to the desired cancer-suppressing effect. On the other hand beta-estradiol is extremely elevated, suggesting a role for this in the cancer's progression[6-10]. The source of the elevation of beta-estradiol is unclear, and whilst unlikely, may be the result of aromatization of testosterone.

There is a clear tendency to formation of clots. Contributing factors are Protein S deficiency, elevated fibrinogen, platelet aggregation and elevated beta-estradiol.

The anemia is probably the result of ongoing inflammation (anemia of chronic disease) and not iron deficiency. There is an accumulation of some toxic substances, probably from exposure to cigarette smoke and certain petro-chemicals. Detoxification processes also appear to be impaired. Antioxidant levels are below normal as are the anti-inflammatory nutritional fatty acids.

Brain neurotransmitters are at trace levels. This is partly due to insufficient pre-cursors but also to neurotransmitter destruction and interference by several false neurotransmitters and neurotoxins. These are most likely the result of viral infection (evidenced by elevated non-genomic rna/dna levels) as well as fungal infection (evidence by elevated tartaric acid).

Serum levels of copper are elevated – a common finding in chronic inflammation and some cancers. Urinary met-enkephalin (OGF) levels are elevated as is serum CD10 gene expression. Whilst the elevated CD10 is considered beneficial in cancer, it is probably also indicative of inadequate number/sensitivity of OGF receptors.

Intestinal ecology is disturbed. There is a deficiency of some of the beneficial organisms and presence of citrobacter-freundii at a possibly-pathogenic[11] level which could also be an aggravating factor for the cancer[12]. Some mycotic organisms are present at low levels.

Secondary bile acid levels are low. This may be secondary to the microbiological imbalance. Beta-glucuronidase is undetectable – this could result from reduced

enterohepatic recirculation or increased excretion of toxins, steroid hormones or other substances subject to glucuronidation.

Extensive food-allergen and antibiotic/analgesic-allergen testing has revealed only minor IgE mediated reactions, which cannot explain the elevated total IgE levels. These may be the result of either fungal infections (as found in the stool microbiology analysis) or parasitic infection.

TREATMENT OPTIONS – INTRODUCTION

Dr. Xxxxx has in the past responded well to androgen-suppressive hormonal therapy. This positive response usually translated into a rapid decline of PSA and reduction in size of some lymph nodes – particularly those in the neck. However, whilst his PSA still declines in response to the therapy, radiological and clinical findings indicate disease progression.

Recent radiological findings have demonstrated progressive hydronephrosis. In the course of the past 3 years Dr. Xxxxx has experienced a number of episodes of DVT or DVT-like symptoms, as well as extensive fatigue and cognitive impairment.

The opportunity has not arisen to measure cellular COX-2 expression. Being that prostate cancer generally leads to over-expression of COX-2, it is reasonable to assume that elevated levels are being produced. Elevated COX-2 levels have been shown to impair lymphatic contractile function which also results in edema.

It is my opinion that primary focus should be placed on the following strategies:

- Suppressing ACE-II and/or blocking ACE-II receptors
- Suppression of bradykinin and other anti-inflammatory measures
- Restoration of p53 function
- Hormonal manipulation
- Restoration of normal gut ecology
- Multi-modal anti-coagulant therapies
- Restoration of neurotransmitter levels
- COX-2 suppression
- Support of detoxification processes
- Renal support
- Correction of nutritional imbalances

Whilst it is possible to select only some of the options and implement them in a limited fashion, I would suggest that initially it is best to pursue a combination of all the options which are deemed compatible and provided they are well tolerated.

TREATMENT OPTIONS

Item 1

Name: ACE-II Receptor Blocker - preferably Candesartan (losartan, irbesartan, olmesartan, candesartan, velmisartan, valsartan, telmisartan) perhaps combined with an ACE inhibitor.

Dose: Candesartan 4mg – 8mg daily or regular therapeutic dose for other drugs

Rationale: ACE-II levels are extremely elevated. ACE-II is a growth factor for prostate cancer[1-3,13,14]. ACE-II receptor blockade has been demonstrated to suppress prostate cancer growth both pre-clinically and clinically, even in hormone refractory prostate cancer[3,13]. It may be beneficial to combine An ACE-II receptor blocker with an ACE-Inhibitor which may perhaps achieve a superior and synergistic effect. Candesartan is poorly absorbed however it is the only ACE-II receptor blocker which has been used clinically in prostate cancer[3,13]. Blocking the action of ACE-II may also be protective for the kidneys which are presently at risk.

Item 2

Name: Noscapine

Dose: 20mg three to four times daily, every 4 – 5 hours.

Rationale: Suppression of bradykinin which is extremely elevated. Bradykinin serves as a growth factor for prostate cancer[15-17]. Targeting ACE-II receptors also leads to an elevation in bradykinin which can negate the beneficial effect[4,5]. Noscapine has been clinically demonstrated to effectively block bradykinin[18-20], as well as ACE-inhibitor induced cough which results from increase in bradykinin[21].

Item 3

Name: Metformin

Dose: 500mg twice daily (preferably slow release).

Rationale: Inhibits growth of p53 deficient cells[22]. Metformin is being studied for its anti-cancer effects[22-25] which have long been known from retrospective data. It also indirectly inhibits action of insulin-like growth factor[24] which is associated with growth of prostate cancer[26-28].

Item 4

Name: Ketoconazole + Hydrocortisone

Dose: Ketoconazole 200mg two to three times daily, hydrocortisone 20 – 40mg in the morning, 10 – 20mg in the evening. Ketoconazole should be taken with an acidic beverage to increase absorption.

Rationale: This combination has been found to be effective in treating hormone refractory prostate cancer[29-34]. Some studies have used low dose (200mg thrice daily) and others high dose (400mg thrice daily). The ketoconazole should also assist in eliminating the intestinal fungal infections. The hydrocortisone is given primarily to replace cortisone due to adrenal suppression by ketoconazole. However, it has its own independent anti prostate cancer effects[35-37]. Dose requires personal adjustment. Prednisone or Prednisolone (at an adjusted dose) has been used in some studies[29], but hydrocortisone is believed to be superior.

Item 5

Name: VSL#3 Probiotics (sachets) + Lactobacillus Reuterii (capsules)

Dose: As tolerated.

Rationale: Both these products have undergone extensive clinical trials and have demonstrated ability to populate the GI tract, correct microbiological imbalance, eradicate pathogens, eliminate IgE-based allergies and positively influence immunity by reducing opportunistic infections as well as increasing overall health[38-101].

Item 6

Name: Dipyridamole Retard

Dose: 200mg once or twice daily

Rationale: Inhibitor of platelet aggregation which is a prime cause of elevated platelet-derived-growth factor. Potent anti-viral effect[102-106], anti-cancer effects[107-112]. Synergistic with interferon alpha[113,114] (which is induced by Imiquimod) and reversal of multi drug resistance[115-117].

Item 7

Name: Selegiline

Dose: 5mg orally either daily or every 2nd day, or preferably transdermal (available in USA as "EMSAM" 6mg every 2nd day).

Rationale: MAO-B inhibitor, restoration of neurotransmitter function, normalization of neuroendocrine-immune responses, anti-cancer effects[118-123].

Item 8

Name: Imiquimod (Aldara) topical application, oral use, or both.

Dose: 2 sachets rubbed on skin near swollen lymph nodes twice weekly + 50mg orally twice weekly (with food). Rub on different areas to prevent skin irritation.

Rationale: Induction of OGF-receptor expression[124]. Induction of interferon-alpha and potent antiviral[125-127]. anti-tumor[125,128] and anti-angiogenic[129] effects. Systemic effects seem to be achieved via topical administration. Oral administration in capsules is possible[130-133] but at low dose in order to prevent gastric irritation. Preclinical trials examining systemic anti-tumor effects suggest that twice weekly use is as effective as daily use[130].

Item 9

Name: Kremezin (AST-120) (Beaded Activated Carbon from Petrolium Pitch)

Dose: 4 -5 grams twice daily, should be taken at least 1 hour after ACE-II receptor blocker.

Rationale: Renal support, prevention of renal deterioration, binding of uremic toxins, adsorption of intestinal toxins[134-161].

Item 10

Name: Parthenolide (extract of feverfew)

Dose: 4mg – 8mg each evening, either by mouth with some fat or transdermally.

Rationale: Inhibitor of platelet aggregation[162,163], eradication of cancer stem and progenitor cells[164-168], inhibitor of nuclear-factor kappaB[169-172] which is a driving factor in prostate cancer progression[173]. Additionally, this should achieve inhibition of the COX-2 enzyme[174-176], IL-6 and IL-8. This dose has been used safely in treating headaches.

Item 11

Name: Piracetam

Dose: 4 – 8 grams daily in 3 divided doses

Rationale: Reduces platelet aggregation[177,178], reduces fibrinogen[179-181], enhances cerebral oxygenation[182-186] which may be compromised due to low VEGF, inhibits of tumor metastasis[187-189].

Item 12

Name: Silibinin Plus® (Life Extension)

Dose: 1 capsule morning and evening with food

Rationale: Liver and detoxificationsupport[190-197], antiproliferative effects in prostate cancer[198-210].

Item 13

Name: Cynarol® (Flora) – Artichoke Fresh Plant Concentrate

Dose: 2 capsules morning and evening with food

Rationale: Liver & detoxification support[211-216].

TREATMENT OPTIONS – CORRECTION OF NUTRITIONAL IMBALANCES

Name: Complete B-Complex® (Life Extension)

Dose: 1 morning and evening with food.

Rationale: Correction of organic acid imbalances, lowering of homocysteine, reduction of clotting risk (folic acid).

Name: Super GLA/DHA® (Life Extension)

Dose: 2 capsules twice daily with food.

Rationale: Correction of fatty acid deficiency.

TREATMENT OPTIONS – SYMPTOMATIC

For Penoscrotal Oedema

Name: Leech therapy.

Availability: Department of Urology, Arrowe Park Hospital, The Wirral, UK

Rationale: Successful trial reported for penoscrotal edema in hormone-refractory prostate cancer patients

Additional Suggestions

Exercise which has been shown to be effective in promoting lymphatic flow and drainage could be of benefit. Specifically this involves rebounding.

Several low level laser therapy devices have been developed which are used to improve lymphatic flow and treat stasis and edema. These are available from specialist suppliers.

DIETARY & LIFESTYLE CONSIDERATIONS

- Ensure adequate fluid intake – 8 – 10 glasses per day.
- Try to avoid foods shown to provoke inflammatory/allergic response, namely: Broccoli, Brussels sprouts, Cabbage, Potato, Pork and foods containing E210 benzoate.
- Avoid hydrogenated fats.
- Avoid vegetable oils when possible, with exception of cold-pressed canola oil, cold- pressed olive oil and cold-pressed grape-seed oil.
- Try to eat berries (fresh or dried), in particularly blueberries and cranberries, for phytochemical and bioflavonoid benefits as well as anti-infective for urinary tract.
- Avoid sugar whenever possible.
- Avoid dairy products if possible (other than whey).
- Avoid processed foods whenever possible.
- Avoid cooking in stainless steel utensils.
- Avoid cooking in copper utensils.
- Ensure excellent ventilation of home at all times to reduce chemical exposures.
- Avoid contact between foods and plastics.
- Avoid using any petroleum-based detergents or soaps.
- Avoid exposure to sources of phthalates.

MONITORING

SYMPTOMATIC

It is to be hoped that symptomatic benefits will be visible within 2 weeks. If none are visible within 4 weeks, it would be prudent to reconsider the direction of therapy.

Specific areas where one should expect quick symptomatic improvement is edema and energy levels followed by a reduction in lymph node swelling.

Any unusual symptoms or possible side effects of medications or supplements should be reported immediately.

FOLLOW-UP TESTS

The following tests should be performed 4 weeks after starting this program and after that at monthly intervals:

CBC
Fibrinogen
PSA
Total and Free Testosterone
Estradiol (E-2)
Urinary Neuropeptides (initially after one month, then every 2 – 3 months)
Urinary Neurotransmitters (initially after one month, then every 2 – 3 months)

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