

PERSONALIZED TREATMENT OPTIONS REPORT

PREPARED ESPECIALLY FOR
MR. XXX XXXXXXXX

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INTRODUCTION

Mr. Xxxxxxx (born 1959) was diagnosed in September 2008 with a poorly differentiated adenocarcinoma in the lung – signet ring cell subtype, presumed to be a lung primary.

A PET/CT Scan performed on 23 Nov 08 showed a lesion of 5.5cm x 6cm in upper left lung (significantly bigger than at initial diagnosis in September) with some pleural effusion, spread to lymph nodes and suspected spread to left adrenal gland as well as bone.

Due to the low curative rate of chemotherapy for this condition and due to his weak constitution, Mr. Xxxxxxx has opted to forego chemotherapy at this point in time. Instead he opted to try Tarceva in the hope that he carries a Tarceva-sensitive EGFR mutation. Furthermore he has had extensive gene analysis performed on blood as well as urinary neurotransmitter and neuropeptide analysis. The purpose of these tests is to shed light on the environment which is influencing tumor growth and spread thereby identifying targets for manipulation in the hope that this will lead to an environment less conducive to tumor growth.

What follows is an overview of the findings and a selection of those options deemed to be most appropriate in this situation with the rationale for each. These are chosen primarily for their ability to target the abnormalities identified as well as their favorable risk-benefit ratio. 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 Mr. Xxxxxxx's physicians.

DIAGNOSTIC OVERVIEW

HISTORICAL FINDINGS

Mr. Xxxxxxx has a generally weak constitution with a history of irritable bowel syndrome suspected related to infective yeast organisms. He has followed several dietary regimens over the years. On occasion his liver function tests have shown an elevation of bilirubin, assumed to be idiopathic.

Over the past year and prior to diagnosis he has experienced two occurrences of pneumonia (without fever). He suffers from hypotension (100/60).

He has suffered from sleep apnea in the past. He reports a previously positive breath test for helicobacter pylori.

His weight has been stable (55 k.g. – height 1.62m) and he is otherwise asymptomatic.

LABORATORY FINDINGS

Results in black = positive findings

Results in red = negative findings

General

- ↑ Homocysteine 8.94 umol/L
- ↓ Vitamin D 20.9
- ↑ Total IgE 189
- ↑↑ CEA 1400
- ↑↑ CA125 243
- ↑↑ EBNA Igg 270
- ↑↑ Bilirubin (Total 2.12 – Indirect 1.90)

Cytokines & Growth Factors

- ↑ p53 Protein Level
- ↑↑ p53 Gene Expression
- ↑↑ BAX Gene Expression
- ↑ p21 Gene Expression
- ↑↑ IL-2 Gene Expression
- ↑↑ EGFR Soluble Level
- ↓↓ Survivin Gene Expression (not detectable)

- ↑↑ TM-2PK Gene Expression
- ↑↑ IL-6 Gene Expression
- ↑↑ TNF- α Gene Expression
- ↑↑ VEGF Gene Expression
- ↑↑ PDGF Gene Expression
- ↑↑ Non-Genomic DNA + RNA Levels
- ↓ IFN- α (not detectable)
- ↓ Dextrorotatory Lactic Acid Level
- ↓↓ CD10 (Neprilysin) Gene Expression

Neurotransmitters and Neuropeptides (urinary)

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

Neurotransmitter Precursors

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

Neurotoxins and False Neurotransmitters

Tartaric Acid - High

Neuropeptides

↑↑ Bradykinin
↓↓ Met-Enkephalin
↑↑ Neurotensin

SUMMARY OF FINDINGS

The diagnostic findings present a very unusual picture. There are no mutations of the p53 gene or the p21 gene and both appear to be functional. Pro-apoptotic BAX is well elevated and BCL-2 is low thus signifying excellent potential for apoptosis to occur. Survivin is absent which is an unusual finding in metastatic disease.

On the other hand there is hyper-glycolysis signified by the elevated TM-2PK and this is probably responsible for the rapid growth rate of the tumor. There is a lot of underlying inflammation signified by elevations in IL-6, TNF- α , platelet derived growth factor and bradykinin.

Angiogenesis is very active signified by elevated VEGF levels and is probably aggravated by hypoxia.

A suppressive growth factor - OGF (met-enkephalin) is totally absent. CD10 is absent too, which signifies the lack of OGF but possibly also absent OGF-receptors. Correcting this abnormality may require increasing production of receptors in addition to replenishment of the ligand.

Bradykinin and neurotensin levels are highly elevated. Both of these contribute to vasodilation and hypotension.

The greatly elevated levels of platelet derived growth factor are indicative of hyper-coagulation. PDGF levels can be lowered by reducing platelet aggregation.

There is abnormal glucose utilization. Elevated neurontin leads to elevations in glucose and insulin resistance.

There appears to be adrenal insufficiency signified by lack of adrenaline in the urine. This leads to reduced oxygenation in the brain. Increasing adrenaline is essential in order to reduce hypoxia (which is also responsible for elevation of VEGF). This can be achieved by increasing nor-adrenaline levels and one way of doing so is through daily exercise such as walking.

The dopaminergic system which is crucial for anti-cancer effects requires activation. The serotonin system needs to be activated simultaneously in order to prevent induction of auto-immunity or auto-antibodies.

There is a very strong viral process signified by the grossly elevated levels of non-genomic RNA and DNA. This viral process is probably the prime reason for destruction of neurotransmitters. There is an absence of natural anti-viral response (signified by absence of interferon-alpha). EBNA antibody levels were elevated and EBV has been implicated in the pathogenesis of signet-ring cell tumors. When implementing treatment, it is essential to pursue an anti-viral approach.

It is important to try and verify whether the tumor is EBV related through more extensive pathological analysis. There is a relatively non-toxic protocol developed at Dana Farber Cancer Institute to treat EBV related malignancies. This protocol, comprising arginine butyrate designed to activate the EBV (which is usually in latent state) followed by ganciclovir has resulted in complete remissions in a high percentage of treatment-resistant malignancies¹⁻⁵.

Another agent which is sometimes effective against EBV in its latent state is cimetidine^{6,7} (or ranitidine). It is also known for its anti-cancer effects. My concern in using it is that long term administration leads to hyper-prolactinemia which may encourage tumor growth. It could be that a short-term therapeutic trial would be beneficial.

The anti-viral approach detailed below has assumed that the respective agents will be effective against viruses even in latent phase. However this should be verified by testing non-genomic RNA/DNA levels 2 weeks after starting treatment. If there is suboptimal effect, it may be useful to use an agent such as arginine butyrate in order to activate the virus/es and therefore make it susceptible to anti-viral therapies.

TREATMENT OPTIONS – INTRODUCTION

On 29th November Mr. Xxxxxxx began taking Tarceva. Within a few days he developed a rash which is considered a sign of beneficial response. His tumor markers which had been constantly and rapidly rising, have declined by approximately 20% during these few days. His unconjugated bilirubin has doubled to twice the maximum normal however there have not been any other significant changes in liver enzymes.

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

- Anti-EGFR
- Anti-Viral Strategies
- Anti-Inflammatory Strategies
- Suitable Anti-Coagulant Strategies
- Normalization of Neurotransmitter Activity
- Liver Support

I would suggest initially pursuing a combination of the following items: 1, 2, 3, 4, 5, 6, 9 & 10 and monitoring for adequate response.

TREATMENT OPTIONS

Item 1

Name: Vitamin D drops (1000iu/drop) – (Pure Encapsulations)

Dose: 6 drops morning, 6 drops evening with food

Rationale: Replenishment of very low Vitamin D levels. Anti lung cancer effects.⁸⁻¹⁶

Item 2

Name: Noscapine

Dose: 25mg x 4 daily with or without food (approximately every 4 – 5 hours)

Rationale: Inhibition of bradykinin¹⁷⁻²⁰ which is extremely elevated. Noscapine can also be used at high dose (1,000mg – 2,000mg daily) for its anti-cancer effect as an anti-tubulin agent.²¹⁻³⁴ However, it requires hepatic metabolism and it would be prudent to first see the effects of Tarceva on the liver.

Item 3

Name: OGF (Met-Enkephalin) Injections

Dose: 60mcg/k.g. injected subcutaneously twice daily or 200mcg/k.g. IV twice weekly. This medication should be taken after eating/drinking. If infused IV, it should be given in 500cc of saline initially over 2 hours, and subsequently can be gradually reduced to 30 minutes provided no symptoms of paresthesia or hypotension develop.

Rationale: Anti-cancer agent³⁵⁻⁴⁸ as well as anti-angiogenic^{49,50}. Replenishment of non-existent methionine-enkephalin. This medication will also boost CD10 levels^{51,52} which has a potent effect against NSCLC⁵³⁻⁵⁶. The beneficial effect of OGF is mediated through its binding to the OGF receptor in tumor cells. There could possibly be a receptor deficiency and in this case it would be advisable to administer Imiquimod which has been shown to exert its anti-cancer effect through stimulation of cellular OGF receptor synthesis⁵⁷. Imiquimod can be given orally at a low dose, but it may be preferable to give it topically (Aldara) with a little DMSO and apply at different locations in order to prevent skin irritation.

Item 4

Name: Disulfiram

Dose: 40mg x 2 daily

Rationale: Lowers TNF-alpha^{58,59}. Anti-cancer and anti-angiogenic effects⁶⁰⁻⁶⁹. Currently in Phase 2 trials for NSCLC at Hadassah^{70,71}. Very well tolerated at this dose. Alcohol should be avoided whilst on Disulfiram.

Item 5

Name: Dipyridamole (Persantin) RETARD

Dose: 200mg once daily (if not available then use Cardoxin Forte 75mg x 3 daily)

Rationale: Inhibitor of platelet aggregation which is a prime cause of elevated platelet-derived-growth factor. Potent anti-viral effect⁷²⁻⁷⁶. Anti-cancer effects⁷⁷⁻⁸². Synergistic with Interferon alpha^{83,84}.

Item 6

Name: Interferon Alpha (Roferon) – low dose

Dose: 300,000 units injected subcutaneously every 2nd evening, in early evening hours.

Rationale: Replenishing non-existent interferon alpha levels. Anti-viral effects⁸⁵⁻⁸⁸, anti tumor effects when used at low doses. This dose is based on the experience of integrative physicians in the USA and UK and is less than 10% of the dose usually used in malignancies. No side effects should be expected with the exception of possible (beneficial) immune reaction at site of injection.

Item 7

Name: Pentoxifylline (Trental)

Dose: 400mg x 3 daily

Rationale: Lowers VEGF⁸⁹⁻⁹¹, IL-6⁹²⁻¹⁰¹ and TNF-alpha¹⁰²⁻¹¹⁷

Item 8

Name: Doxycycline

Dose: 20mg x 2 daily (preferably without food)

Rationale: Lowers VEGF¹¹⁸, IL-6¹¹⁹⁻¹²¹ and well studied anti-cancer effects through suppression of MMP's. At this dose it does not adversely affect the gut ecology¹²².

Item 9

Name: Zoledronic Acid (Zometa)

Dose: Infusion once monthly as prescribed.

Rationale: Prevention of bone metastases as well as diverse independent anti-cancer effects in NSCLC and other cancers¹²³⁻¹²⁶.

Item 10

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, normalization of neuroendocrine-immune responses, anti-cancer effects¹²⁷⁻¹³³. At this low dose it is very unlikely to exacerbate hypotension.

LIVER SUPPORT

The following non-pharmacological agents are recommended for liver support. All of them have hepato-protective or hepato-regenerative properties.

Item 11

Name: Silibinin Plus® (Life Extension)

Dose: 1 capsule morning and evening with food

Item 12

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

Dose: 2 capsules morning and evening with food

Item 13

Name: Calcium-D-Glucarate (Tyler or other brand)

Dose: 500mg twice daily with food

Item 14

Name: Alpha Lipoic Acid Sustain

Dose: 1 tablet in the morning and evening with food

Additional Suggestions

It is essential to avoid citrus fruits whilst using Tarceva. Antifungals should be used with caution whilst using Tarceva.

It is advisable to avoid dietary sources of tartaric acid as it acts as a neurotoxin. Its increased level is probably the result of elevated intestinal yeast levels (signified by elevated Total IgE levels).

Daily consumption of organic mixed berries (blueberries, mulberries and cranberries) is recommended. 24 hour fermented yogurt (preferably from goats or sheep milk) would be beneficial both as an anti-yeast remedy as well as increasing production of neurotransmitters.

Adequate protein should be consumed in order to provide sufficient tryptophan for production of neurotransmitters.

Both a multi-vitamin and a multi-mineral should be taken daily. Suitable choices are Biocare's Adult Multivitamin (1 capsule daily) and Vital Nutrient's Multi-Mineral(4 capsules daily).

GENERAL DIETARY & LIFESTYLE CONSIDERATIONS

- Ensure adequate fluid intake – 8 – 10 glasses per day.
- Avoid hydrogenated fats.
- Avoid vegetable oils when possible, with exception of cold-pressed canola oil, cold pressed olive oil and coconut oil (for its anti-viral effects).
- Avoid sugar whenever possible.
- 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.

MONITORING

SYMPTOMATIC

Monitor blood pressure regularly.

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

FOLLOW-UP TESTS

Tumor Markers
LDH
Liver Function

Repeat Neurotransmitter Profile 4 weeks after starting program in order to monitor changes. Repeat non-genomic RNA/DNA levels 2 – 4 weeks after starting program in order to monitor changes.

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