

**Gurdev Parmar ND¹, FABNO, Erin Rurak ND¹, & Ferdinand Buencamino MD¹
Integrated Health Clinic, Fort Langley, British Columbia¹**

**Case Study: Metastatic Triple Positive Breast Cancer Management With
Capecitabine, Herceptin & Integrated Health Clinic Approach**

Introduction:

Breast cancer is the most common cause of cancer mortality in females¹. Roughly half of all women diagnosed with breast carcinoma develop metastatic disease. Life expectancy varies from 18-30 months with a 5-year life expectancy of 26% in metastatic disease². Standard first line treatments for metastatic breast cancer generally consist of chemotherapy, radiation, and when indicated, hormone blockade. Side effects of the aforementioned treatments can be substantial, leaving some patients fearful and resistant to recommended conventional treatments. In this report, we present a case of a woman diagnosed with metastatic triple positive breast carcinoma, treated at Integrated Health Clinic (IHC). The treatment consisted of conventional treatment with concurrent loco-regional hyperthermia and disease-specific dietary, supplementary, injection and intravenous therapies. We review the application of hyperthermia in conjunction with capecitabine and Herceptin, in a female patient with an aggressive HER2 positive metastatic breast cancer, who refused initial primary treatment suggestions by her medical oncologist.

Case history:

We present the case of NB, a 43-year-old female diagnosed with invasive ductal carcinoma of the right breast, in November 2012. She initially presented with a palpable mass in her left breast in February 2012. Bilateral mammography and ultrasound examinations done in September 2012, confirmed the presence of a 1.7cm nodule within her left breast. Ultrasound examination reported a mass measuring 3.2 x 3.3 x 2.1 cm, with multiple micro-calcifications, within the left breast. It was found at the 1 o'clock position and 4 cm from the nipple. Multiple lymph nodes were noted in the left axilla. A core needle biopsy was also completed in September 2012, confirming a high-grade invasive breast adenocarcinoma, ductal type, ER 2+, PR 1+ and HER-2/neu 3+. There was also a locus of grade 3 ductal carcinoma in situ (DCIS) of the solid type identified, also in the left breast.

NB underwent a lumpectomy and sentinel lymph node resection in October 2012. With one of the five lymph nodes positive for metastatic deposits, NB was diagnosed with stage IIB (T2N1MX), triple positive, infiltrating ductal carcinoma in the left breast. Clear margins were not obtained and a thus second surgery was completed in order to clean up the positive margins. Standard adjuvant chemotherapy consisting of 5-FU, epirubicin, and cyclophosphamide followed by docetaxel was

then recommended by her medical oncologist. NB declined this initial systemic treatment recommendation due to concerns of possible side effects. She did however begin the prescribed tamoxifen at 20mg, and she also received the recommended radiation treatment given over 5 weeks. A follow up bone scan and CT scan of the chest, abdomen and pelvis done on November 2012 were clear at this time.

NB was under the initial care of another healthcare provider in November 2012, when she presented as a thin patient with no reported evidence of lymphadenopathy. Heart, lung, and abdominal exams were reported as unremarkable. The right breast was reported clear of any palpable masses and the left breast showed a large resolving hematoma. This practitioner appropriately advised NB to receive the chemotherapy recommendation given to her for the invasive breast cancer. She again declined adjuvant chemotherapy, but did continue on naturopathic treatment consisting of intravenous ascorbic acid (25 gram) twice weekly and targeted supplementation (Table 1.)

Table 1. Initial Prescription & Supplements from Other Provider

| Medications | Dosage | Effect |
|--|---|---|
| Prescriptions | | |
| Metformin | 500mg p.o. QD | Induces AMPK activation decreases insulin levels and leads to inhibition of protein synthesis pathways, decreasing cancer cell proliferation ³ . Decrease insulin (promotes cancer cell growth) resistance and reduces insulin level. Direct inhibitory effect on cancer cell growth and antitumoral action ⁴ |
| Supplements | | |
| Can-Arrest Boswellia Curcumin Quercetin | Boswellia 200mg Curcumin 200mg Quercetin 100mg 2 capsules p.o. BID | Inhibition of the transcription factor NF-κB to arrest tumor growth and its progression ⁵ . Anti-inflammatory and antioxidant activity causing inhibition of vascular endothelial growth factor-mediated angiogenesis in human intestinal |

| | | |
|----------------------|---------------------|---|
| | | microvascular endothelial cells ⁶ |
| Vitamin D | 6,000 I.U. p.o. QD | Role in primary prevention and adjunct to existing treatments for cancer ⁷ . Deficient vitamin D levels in were predictive of a worse prognosis of distant disease-free survival, as well as overall survival ⁸ . |
| Coriolus versicolour | 2 capsules p.o. BID | Anti-tumor, immunomodulation ⁹ . Immunomodulation resulting in tumor destruction ¹⁰ |
| ProEPA | 2 capsules p.o. QD | Anti-cachectic effect ¹¹ . Help in both prevention and management of breast cancer ^{12,13} |
| Melatonin | 20mg p.o. QHS | Multi-disciplinary anti-cancer action reduces toxicity after chemotherapy, radiotherapy, immunohormonal therapy and cancer surgery. Adjuvant therapy for cancer ¹⁴ . Immunomodulatory in the immunocompromised state ¹⁵ . |

NB remained on this treatment plan until July 2013 when she presented to her family doctor with acute abdominal pain, fatigue and hepatomegaly. An abdominal ultrasound done in July 2013 identified multiple hypo-echoic masses within the liver, with the largest in the right lobe measuring 4.5 x 2.8 cm. A follow-up CT scan was then done, confirming a significant burden of hepatic metastatic disease (Fig. 1, 2, 3).

Figure. 1 -CT scan of abdomen & pelvis - July 2013



Figure 2. - CT scan of abdomen & pelvis - July 2013

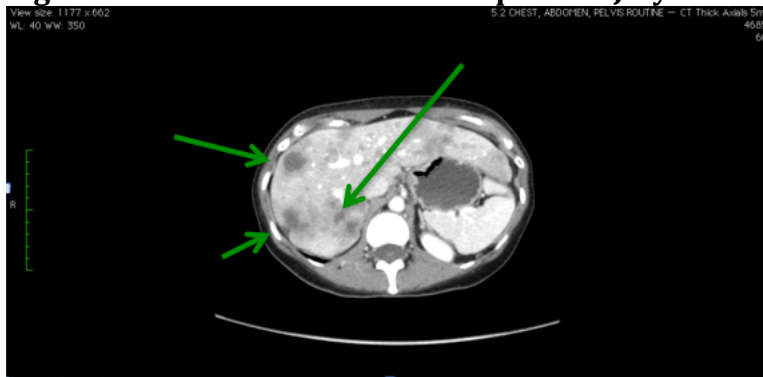
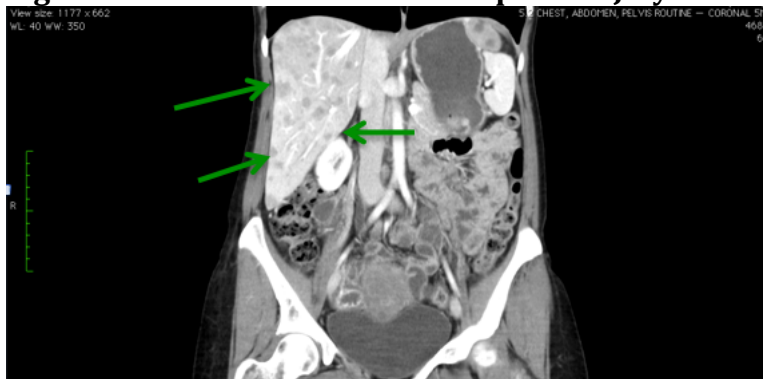


Figure 3. - CT scan of abdomen & pelvis - July 2013



Given the progression of her disease, NB received a second opinion from a naturopathic physician at IHC in August 2013; who also referred her to another medical oncologist for another opinion. Along with her new stage of disease, her primary symptomatic concerns were abdominal pain, malaise and fatigue. On physical exam, a tender abdomen with a palpable liver border in the right upper quadrant and epigastrium was noted. Several chemistry enzymes as well as breast-specific tumour markers were significantly elevated (GGT-132, ALT-115, AST-154,

LDH-274, Alk Phos-111), CA 15-3 (1192), CA-125 (78). Liver biopsy found that her pathology had now changed from triple positive, to ER+ and HER2+. Given the significant progression and burden of disease, it was recommended that NB follow a treatment plan consisting of both conventional therapy and integrative naturopathic interventions. There is growing evidence that integrative naturopathic treatments can both improve potential benefits of conventional treatment, and minimize their potential side effects.

NB was agreeable to such an approach, and agreed to a “softer” conventional plan consisting of oral capecitabine 750 mg BID, trastuzumab (Herceptin) every 3 weeks (now having received 26 infusions), and continuing with her previously prescribed tamoxifen, 20 mg QD. A more intensive integrative naturopathic treatment plan was also recommended, including loco-regional hyperthermia (LRHT) (from September 17th-December 13th 2013 for a total of 15 treatments). A large probe placed over the abdomen, spanning T5-L5 vertebral segments, target the liver. Each LRHT treatment was preceded by oral capecitabine and targeted supplementation (Table 2), taken 30-45 minutes before each LRHT treatment. Treatment temperatures ranged from 46.5-46.8°C, with each treatment lasting 60 minutes. Intravenous ascorbic acid (IVAA) was administered during LRHT treatments, and mistletoe lectins (Iscador) were given subcutaneously 30-45 minutes prior to each LRHT treatment.

Table 2. Modified Prescription & Supplement Rx from IHC

| Medications | Dosage | Effect |
|----------------------|-------------------------|---|
| Prescriptions | | |
| Metformin* | 500mg tablet p.o. QD | Induces AMPK activation decreases insulin levels and leads to inhibition of protein synthesis pathways, decreasing cancer cell proliferation ³ . Decrease insulin resistance (promotes cancer cell growth) and reduces insulin level. Direct inhibitory effect on cancer cell growth and antitumoral action ⁴ . |
| Celebrex* | 200mg capsules p.o. BID | Inhibit cyclooxygenase-2 (COX2) enzymes. Blocking COX 2 has been shown to decrease tumor invasiveness ¹⁶ . Induce apoptosis and inhibit angiogenesis of tumor cells ¹⁷ . Thermal sensitizer and |

| | | |
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| | | prevents thermotolerance ^{18,19} . |
| Supplements | | |
| Meriva* | 2 capsules p.o. QD | Lecithinized formulation of curcumin showing improved absorption ²⁰ . Inhibition of the transcription factor NF- κ B to arrest tumor growth and progression ²¹ . Upregulate anti-oxidative responses and downregulate inflammatory pathways ²² . |
| Quercetin* | 500mg capsules p.o. | Pro-apoptotic, anti-proliferative, anti-oxidant and tumor growth suppression ^{23,24} . Inhibit glycolysis, decrease lactate production and increase apoptosis in breast and ovarian cell line models ²⁵ . Inhibits thermotolerance ^{26,27} |
| Melatonin | 20 mg tablet p.o. QHS | Multiple anti-cancer actions including; reduces toxicity after chemotherapy, radiotherapy, immunohormonal therapy and cancer surgery. Adjuvant therapy for cancer ¹⁴ . Immunomodulatory in the immunocompromised state ¹⁵ . |
| IHC Multi-Vitamins | 1 capsule p.o. BID | Raises tissue cofactor concentrations and thereby increases the activity of defective enzymes ²⁸ . Independent protective factor for breast cancer ²⁹ |
| Multi B 6 | 1 capsule p.o. OD | Anti-tumor ³⁰ . Arrest tumor proliferation and induce cell death ³¹ . Prevents hand and foot syndrome caused by Capecitabine ^{32,33} |
| Can-Arrest | 3 capsules p.o. BID | Inhibition of the |

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|------------------------|------------------------------------|--|
| | | transcription factor NF-κB to arrest tumor growth and its progression ⁴ . Anti-inflammatory and antioxidant activity causing inhibition of vascular endothelial growth factor-mediated angiogenesis in human intestinal microvascular endothelial cells ⁶ . |
| Fish oil (Omega 3 oil) | 1 teaspoon p.o. OD | Prevent progression of APPR and cachexia in weight losing patients with advanced cancer ³⁴ . Attenuates breast cancer cell migration/invasion ¹³ . |
| Vitamin C | 6,000mg p.o daily in divided doses | Cytotoxicity toward cancer cells and slow the growth of tumor ³⁵ . Exerts anti-oxidative stress function ³⁶ . |
| Vitamin D3 | 3,000 I.U. tablet p.o. OD | Role in primary prevention and adjunct to existing treatments for cancer ⁵ . Low and decreased levels might correlate with progression and metastasis of breast cancer ³⁷ . |

* Taken orally 30-45 minutes prior to loco-regional hyperthermia

NB was instructed to follow a low glycemic, whole foods diet, with minimal refined sugars and flours. She was instructed to take part in moderate exercise in the form of walking at least 4 times weekly. She responded well to therapies without side effects. Although she had lost weight (from 98 lbs. to 88 lbs.) after radiation and initiation of tamoxifen, her weight stabilized during this multi-modal treatment plan. She reported a continual and sustained improvement to her quality of life over that time period.

A scan performed in December 2013 found a dramatic reduction in hepatic tumour burden from August 2013. (Fig. 4,5,6).

Figure 4. - CT scan of abdomen & pelvis - December 2013



Figure 5. - CT scan of abdomen & pelvis - December 2013

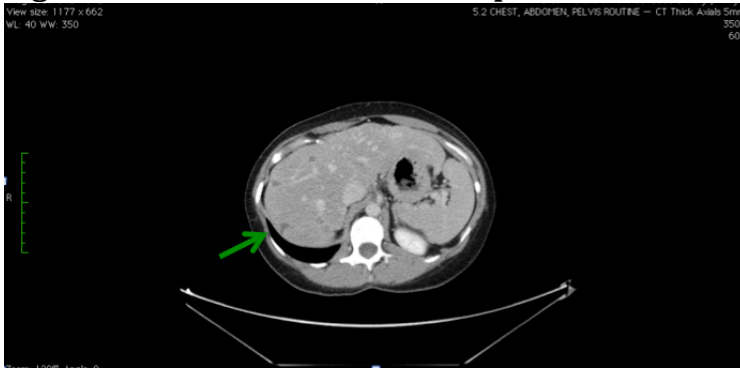
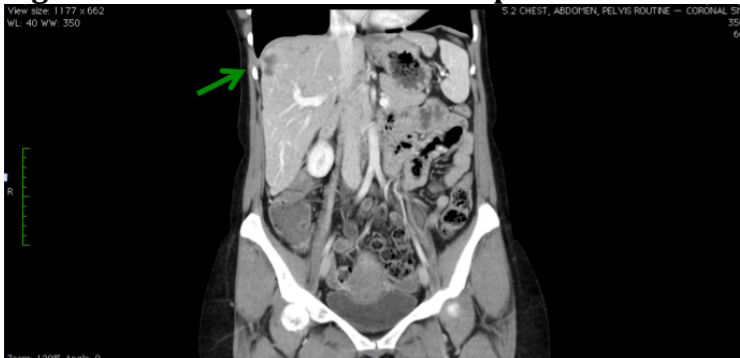


Figure 6. - CT scan of abdomen & pelvis - December 2013



CA 15-3 initially increased from 754 kU/L in July 2013 to 1192 k/UL in September 2013. In April 2014, CA 15-3 decreased to 15kU/L and remained stable thereafter (Chart 1.).

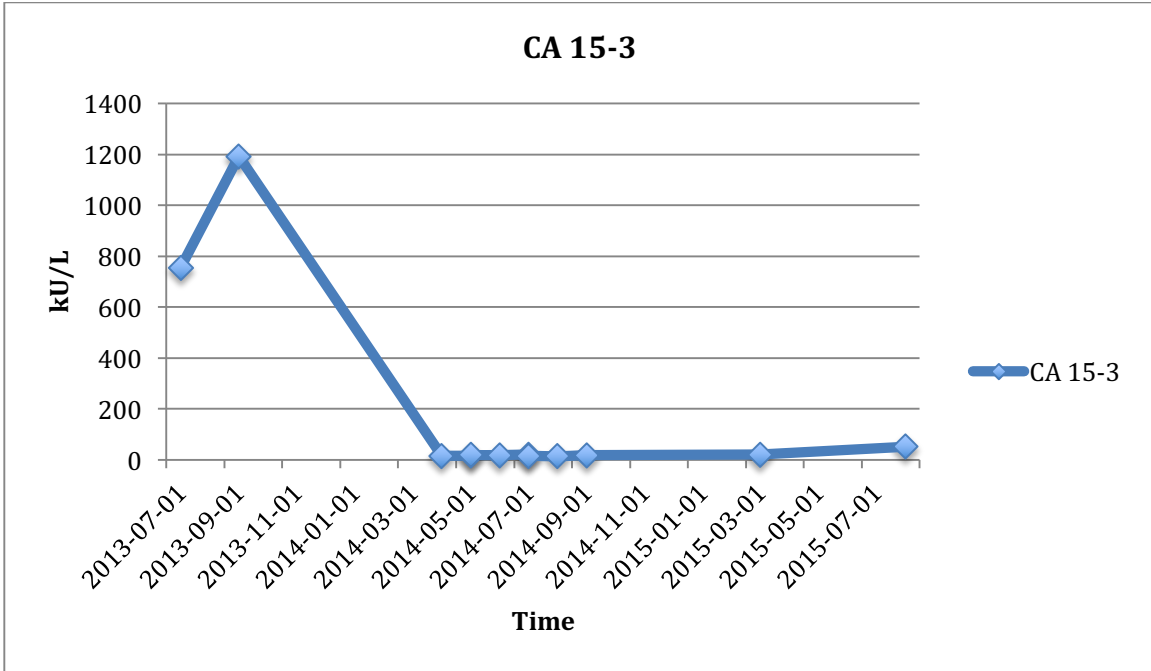


Chart 1. CA 15-3

NB finished her capecitabine treatment in September 2014. Now in November 2015, she continues to feel well without any new symptom developments and no further progression of disease from scan reports. In January 2015, CT of the chest, abdomen and pelvis showed stable appearance. No new liver lesions and no new metastatic findings are seen. Over all appearances are consistent with stable disease. (Figure. 7,8).

Figure. 7 - CT scan of abdomen & pelvis - January 2015



Figure 8. - CT scan of abdomen & pelvis - January 2015



In May 12, 2015, CT of the chest, abdomen and pelvis showed progression of at least two hepatic lesions, additional hypodensities in the liver are unchanged, no intra-abdominal adenopathy, ascites or inflammatory changes. (Fig. 9, 10, 11)

Figure 9. - CT scan of abdomen & pelvis - May 2015



Figure 10. - CT scan of abdomen & pelvis - May 2015

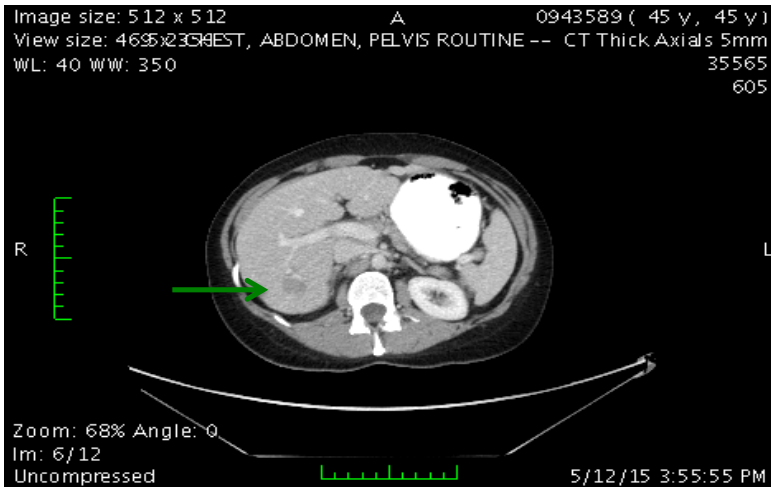


Figure 11 - CT scan of abdomen & pelvis - May 2015



In August 2015, CT of the chest, abdomen & pelvis showed the masses within the liver appear larger. (Figure 12, 13, 14)

Figure 12. - CT scan of abdomen & pelvis - August 2015

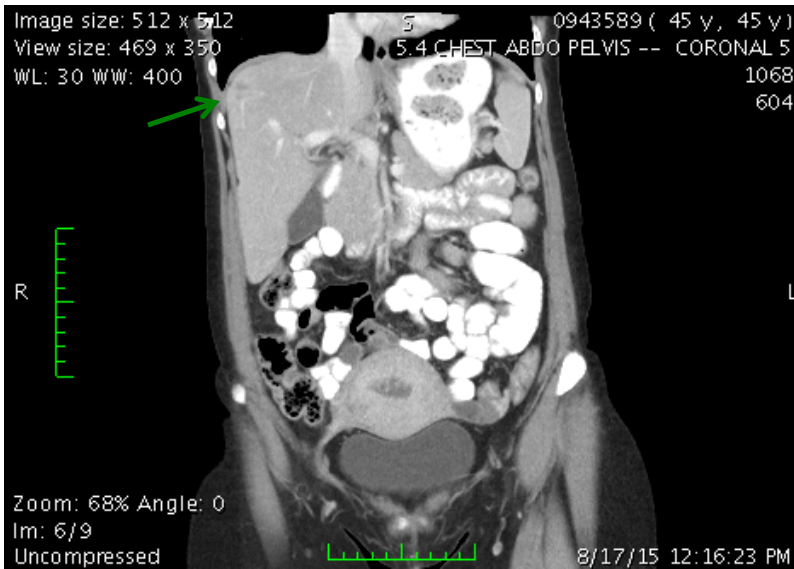


Figure 13 - CT scan of abdomen & pelvis - August 2015

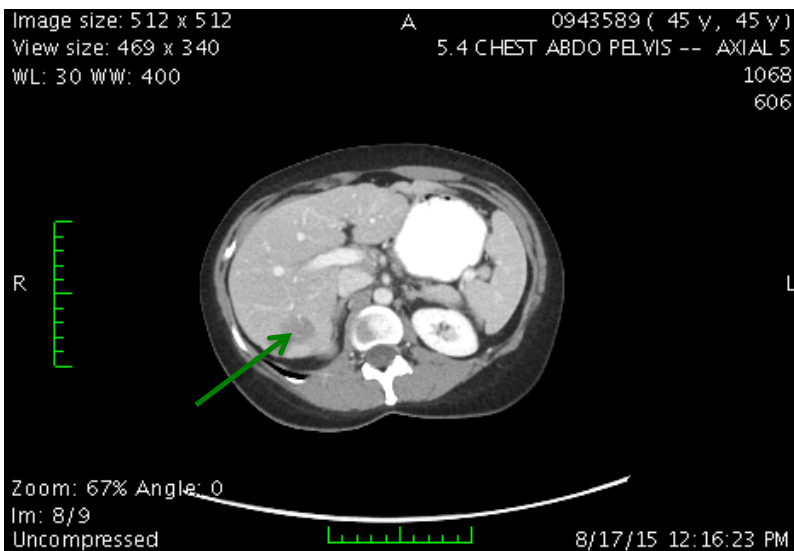
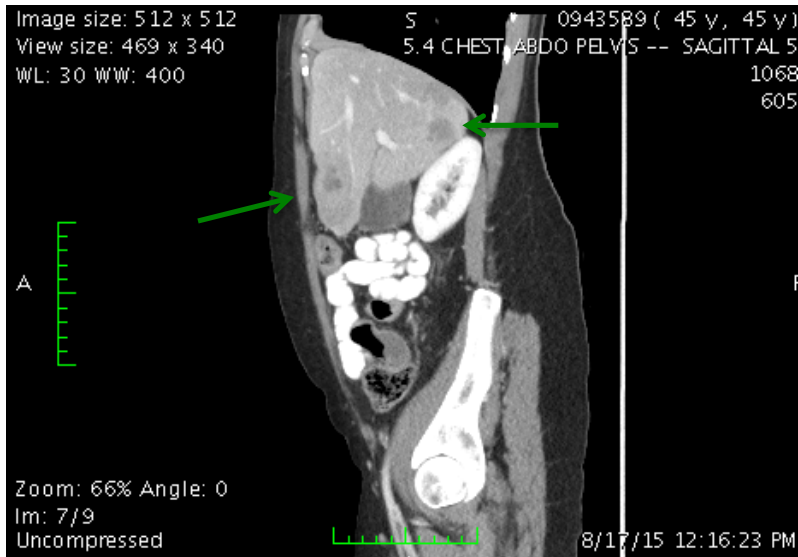


Figure 14 - CT scan of abdomen & pelvis - August 2015



Discussion:

The use of capecitabine, Herceptin, and tamoxifen in combination with naturopathic treatments is proving to be a safe and efficacious management NB's metastatic HER-2 positive breast cancer. Generally, capecitabine and herceptin are used as secondary or tertiary palliative therapy options, after failure with standard chemotherapy protocols such as anthracyclines and or taxanes³⁸. As first line treatment for metastatic breast cancer, overall survival is roughly two years and average time to progression has been documented at 280 days¹.

Hyperthermia is widely used as a cancer modality in Europe and Asia, with impressive safety profiles^{39,40}. The use of hyperthermia monotherapy has provided both partial and complete response rates for several malignancies, including squamous cell cancers, adenocarcinomas and melanomas⁴¹. When cancer cells are subjected to high temperatures (40-43° C), they are susceptible to irreversible damage, in a time and dose dependent way⁴². The application of heat leads to direct tumour cytotoxicity, upregulation of the innate and adaptive immune responses and aids in drug delivery to tumour cells^{2,43,44}. To our knowledge, there have been no studies examining the use of capecitabine and herceptin in combination with hyperthermia. It is known that oral capecitabine, unlike the parenterally administered 5-FU, concentrates primarily in tumour tissue as opposed to healthy tissue and plasma^{2,45}. LRHT also aids with targeted drug delivery³⁷ and thus could have synergistic actions when used with capecitabine. In an overview of methods for drug delivery to tumours, research shows that reduction of tumour interstitial flow pressure (TIFP) was temperature and time dependent. The reduction of TIFP was associated with an increase in perfusion and a sustained reduction of hypoxia, which led to an improvement in antitumoral effects when utilized alongside chemotherapy and radiotherapy⁴⁶.

Targeted supplementation is aimed to address the known hallmarks driving breast cancer. For example, celecoxib has been studied for its use in cancer prevention and treatment. By acting on COX-2, it reduces prostaglandin and thromboxane formation⁴⁷. These inflammatory markers increase angiogenesis and inhibit apoptosis. Blocking their formation can thus promote apoptosis and reduce blood vessel formation to metastatic sites^{22, 48}.

Metformin shows promise as adjuvant therapy in many cancers including breast cancer. The mechanism is not fully clear but is possibly due to the activation of adenosine monophosphate-activated protein kinase (AMPK) leading to the inhibition of protein synthesis and growth of tumour cells⁴⁹. Furthermore, it is well known that chronic inflammation is a contributor to the development and progression of cancer. Metformin reduces inflammatory markers and vascular endothelial growth factors, which are thought to contribute to its anti-cancer and pro-apoptotic pathway⁵⁰.

IVAA at high doses has anti-tumour and chemosensitization effects⁵¹. Studies have demonstrated improvement in quality of life and cancer related symptoms⁵². When present at high plasma concentrations, IVAA generates hydrogen peroxide, a cytotoxic reactive oxygen species. In healthy cells hydrogen peroxide is catabolized to water and oxygen via catalase. Tumour cells lack catalase enzymes leaving malignant cells vulnerable to the cytotoxic effects of hydrogen peroxide²⁶. Tumour cells also take up more ascorbic acid than do healthy cells through glucose transports, which are upregulated due to increased metabolic demand²⁶.

This report demonstrates efficacy and safety of integrative oncology treatments for metastatic breast cancer. Although it is not known to what extent naturopathic approaches played in this patient's treatment, it is known that she handled both conventional and naturopathic treatments without side effects and continues to show regression in a very aggressive metastatic breast cancer.

Conclusion:

This case report shows that naturopathic integrative oncology treatment is safe and effective for the management of metastatic triple positive breast carcinoma. Metastatic breast cancer should be managed as an aggressive disease, utilizing all possible resources with a foundation of safety and efficacy data. Hyperthermia in combination with oral chemotherapy, estrogen receptor antagonist and targeted supplementation has shown to be effective in the management of breast cancer with fewer side effects. The use of an integrative approach to treatment played an important role for this patient's wellness and quality of life.

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