Can Metabolic Therapy of Breast Cancer Outperform Post-Op Adjuvant Chemo and Hormonal Therapy? *In vitro* Analysis and Clinical Correlation

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OVERVIEW

- *in vitro* live cell chemo-sensitivity / chemo-resistance assay can accurately predict the efficacy of various drugs and combinations for cancer therapy
- ChemoFit™ CS/CR assay from Acccutheranostics in Amherst, NY is one such assay which uses fresh live tumour cells, uncultured
- ChemoFit ™ was performed on a 50 year old female at the time of surgery for breast cancer with node mets
- Tumour had multi-drug resistance to chemos but was very sensitive to a combination of metabolic therapies metformin and dichloroacetate
- Assay-guided metabolic therapy alone was administered (no chemo or hormonal therapy)
- Dramatic reduction of circulating tumour cell counts resulted with no serious toxicity
- Subsequent hormonal therapy failed (increased circulating tumour cell counts)
- Re-treatment with same metabolic therapy resulted in rapid CTC reduction again

INTRODUCTION

- The metabolic therapy **dichloroacetate (DCA)** has been shown to kill various human cancers *in vitro* and *in vivo*, including breast cancer
- The diabetes drug **metformin (MET)** has been extensively researched as an anticancer therapy (*in vitro* and *in vivo*)
- Khan and Bradford recently demonstrated the potential widespread role of metformin in cancer treatment using fresh human cancer cells *in vitro:*
- ***Individualizing Chemotherapy using the Anti-Diabetic Drug, Metformin, as an "Adjuvant": An Exploratory Study. J Cancer Sci Ther 5:120-125.***
- Metformin was shown to potentiate various chemos and the metabolic therapy DCA

METHODS

- 50 year old female, lumpectomy for newly diagnosed breast cancer
- Pathology: **invasive ductal carcinoma** with lobular features, 3.5 x 3 x 2.2 cm, margins clear, lymphovascular invasion, **3/5 sentinel nodes positive** (2 macromets, 1 micromets)
- ER+ 95% PR+ 95% HER2 neg, completion axillary dissection, no distant mets
- sample sent at that time for ChemoFit ™ CS/CR assay
- Patient was offered radiotherapy and AC-Taxol followed by tamoxifen – DECLINED
- Treatment monitored with circulating tumour cell (CTC) count (Maintrac ™ Bayreuth, Germany - laser microfluorimetry for human epithelial cell antigen-positive cells)

TREATMENT 1 – oral DCA + oral MET

- **DCA 1000mg po bid** on a cycle of 2 wks on / 1 wk off, with **MET 500mg po tid x** 3 months
- stopped due to grade 2 peripheral neuropathy (known side effect of DCA)
- no other side effects (no decr blood cell counts, no hypoglycemia - patient is non-diabetic)

TREATMENT 2 – LHRH agonist + AI

- Stopped DCA + MET to allow neuropathy to heal
- Attempted laparoscopic oophrectomy: abandoned due to adhesions
- Treated with **LHRH agonist + AI** (aromatase inhibitor: letrozole)

TREATMENT 3 – intravenous DCA + oral MET

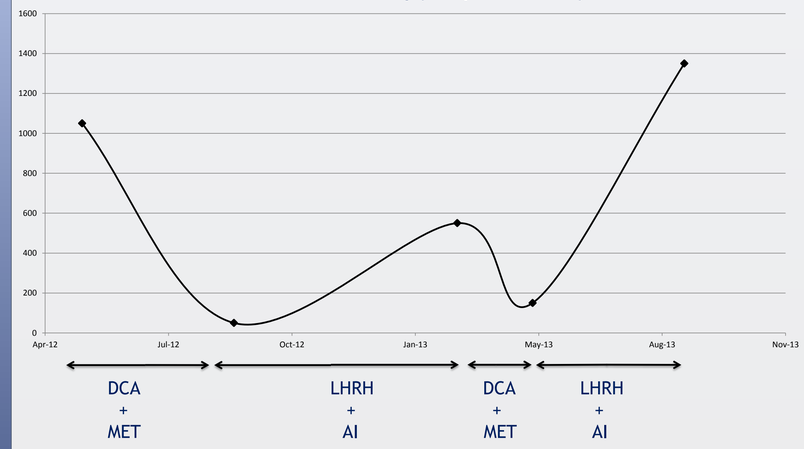
- Neuropathy resolved
- Re-treated with **DCA 3750mg iv 2x/wk + MET** (DCA changed to iv for decr neuropathy risk)
- 3 weeks therapy only (patient had to travel out of country), **no side effects**

RESULTS

ChemoFit™ Assay

DRUG	% Killed/Sensitivity
Taxol	3% LDS
Doxorubicin (Dox)	0% LDS
5-FU	7% LDS
Navelbine (Nav)	18% LDS
Taxotere	0% LDS
Gemcitabine (Gem)	0% LDS
Tamoxifen (Tam)	0% LDS
DCA	21% LDS
Dox / Taxol	0% LDS
Dox / Taxotere	3% LDS
5-FU	0% LDS
DCA / Metformin	**98% HDS** (strong synergism)
DCA / Tam	26% LDS
DCA / Carboplatin	**93% HDS** (strong synergism)
DCA / Cisplatin	12% LDS
DCA / Metformin / Tam	30% LDS (Tam inhibits DCA+metformin)
Carbo / Metformin	26% LDS
Gem / Metformin	0% LDS

Maintrac CTC Assay (cells/ml of blood)



Post-op CTC	1050 cells/ml (detection limit = 10)
Post 3 mo. oral DCA + MET	50 cells/ml
Post LHRH+AI	550 cells/ml
Post 3 wks i.v. DCA + MET	150 cells/ml
Post LHRH+AI	1350 cells/ml

CONCLUSIONS

- Use of live cell CS/CR assay such as ChemoFit ™ may be of great value - with further research this could become standard of care
- CS/CR testing of non-toxic drugs (e.g. metformin, dichloroacetate) alongside conventional chemotherapies, has the potential to revolutionize post-operative adjuvant therapy of breast and other cancers
- Clinical trials of the use of CS/CR assay in the adjuvant therapy of breast cancer should be conducted
- CS / CR assay may be highly cost effective (avoid toxicity / complications from ineffective agents, potential for improved patient outcomes)
- Oral and intravenous DCA may have a significant role in cancer therapy
- Trials involving metabolic / non-toxic therapies are desperately needed to reduce or avoid the use of harmful cancer therapies
- Funding for human trials of generic drugs like DCA and metformin remains a huge challenge
- Patients should be given the option for CS/CR assay to test investigational drugs (e.g. DCA, MET) and use them off-label after understanding the risks and benefits
- We believe **individualized therapy** is the way of the future

AUTHOR BIO

- Completed MD in 1992 certified in Family Medicine in 1994 (University of Toronto)
- Primary practice for the last 20 years has consisted of palliative medicine with a focus on cancer
- Founded the first private integrated cancer center of its kind in Canada (Medicor Cancer Centres) in 2006
- Since 2007, has researched and successfully used several non-toxic off-label cancer therapies
- Over 1300 patients treated with DCA
- Now using the diabetes drug metformin extensively as an adjuvant to chemotherapy
- 4 cancer-related publications in peer-reviewed journals in the last 3 years

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