

## Updated Protocol – 2020 Anderson

### Metabolic Therapies in Advanced “Salvage” Cancer Cases

An excellent example of true therapeutic synergy was discovered in the earlier days of my IV research (under the NIH funded Bastyr Integrative Oncology Research Center) in the combination therapy using Poly-MVA and Dichloroacetate (DCA) for both IV and oral use. We will describe the basis of the synergy and the initial case series that was followed.

Before discussing the combined metabolic therapy we developed it would be useful to discuss the components separately in regard to their use in cancer. Those components are DCA, Retinol, Hyperbaric Oxygen and finally PolyMVA versus Alpha Lipoic Acid.

#### DCA

DCA is a relatively small molecule, which has been used as treatment for lactic acidosis. It inhibits lactate formation and releases pyruvate dehydrogenase kinase from negative regulation, thus promoting pyruvate entry into the TCA cycle. This increases oxygen consumption and reactive oxygen species (ROS) formation while glycolysis and lactate formation are repressed<sup>i</sup>. Non-cancerous human cells prefer this aerobic pathway for energy formation via the electron transport chain (ETC) use. Cancerous cells experience the Warburg Effect where most glucose is converted to lactate regardless of oxygen availability<sup>ii</sup>. Forcing a cancerous cell into TCA / ETC use thereby increases ROS formation and oxygen consumption<sup>iii</sup>.

Cancers targeted in the published data included glioblastoma and are targeted due to their reliance on glucose metabolism, as well as the ability of DCA to cross the blood brain barrier<sup>iv</sup>. Other cancer cell types which have shown sensitivity are breast, prostate, colorectal, pancreatic and endometrial cancers<sup>v</sup>.

The most common toxicity is a dose dependent reversible peripheral neuropathy. Other reactions appear to be mediated by a slowing of glutathione activity via the GSTz pathway: “From the Abstract: Dichloroacetate (DCA) inhibits its own metabolism and is converted to glyoxylate by glutathione S-transferase zeta (GSTz). ... Moreover, DCA-induced inhibition of tyrosine catabolism may account for the toxicity of this xenobiotic in humans and other species.”<sup>vi</sup> As clinically most toxicity effects appear to be mitigated either by slowing infusion, adding glutathione and nutrient support or both the use of such additional measures is indicated.

#### Retinoids

Retinoids (i.e., vitamin A, all-trans retinoic acid, and related signaling molecules) induce the differentiation of various types of stem cells. Nuclear retinoic acid receptors mediate most but not all the effects of retinoids.

Retinoid signaling is often compromised early in carcinogenesis, which suggests that a reduction in retinoid signaling may be required for tumor development. Retinoids interact with other signaling pathways, including estrogen signaling in breast cancer. Retinoids are used to treat cancer, in part because of their ability to induce differentiation and arrest proliferation. “Retinoid research benefits both cancer prevention and cancer treatment.”<sup>vii</sup> Retinoic acid has been investigated extensively for its use in treating different forms of cancer not only in prevention but also in treatment. “Under normal circumstances in the body, retinoic acid does preventive work against cancer formation. After cancer formation, retinoic acid becomes an attacker to cancer cells, one that blocks their growth and division and also triggers their differentiation and death through specific pathways.”<sup>viii</sup>

### **Hyperbaric Oxygen Therapy (HBOT)**

HBOT is widely used as an adjunctive treatment for various pathological states, predominantly related to hypoxic and/or ischaemic conditions. It also holds promise as an approach to overcoming the problem of oxygen deficiency in the poorly oxygenated regions of the neoplastic tissue. Occurrence of local hypoxia within the central areas of solid tumors is one of the major issues contributing to ineffective medical treatment. HBOT alone offers limited curative effect and is typically not used as monotherapy. In most oncology settings HBOT is used as a treatment along with other therapeutic modalities. An excellent review published in 2016 by Ostrowski et.al discusses the recent data regarding safety, efficacy and potential uses of HBOT in oncology and is a highly recommended resource.<sup>ix</sup>

### **PolyMVA**

PolyMVA is a redox molecule that facilitates energy charge transfer at the cellular level with regards to the cellular transport chain, it can therefore protect and provide energy. Mimics the electron transport chain. Differs from free radical scavengers (e.g. alpha-lipoic acid) since there is no free lipoic acid or palladium. They are irreversibly bound together resulting in a molecule that is both fat and water soluble. PolyMVA (also referred to as Pd-LA) is a polymer (liquid crystal) rather than a single molecule. Therefore, the polymer provides a unified redox reaction. In summary it is an extremely effective energy transferring molecule. PolyMVA has been shown to be neuroprotective and helpful in supporting the mitochondrial complex.<sup>xxixixiii</sup>

One reason to consider PolyMVA in a combined therapy is mitochondrial support as this has the potential to aid metabolic therapies by strengthening normal cells and potentially weakening cancer cell metabolism. A study<sup>xiv</sup> looking at the effects of PolyMVA on mitochondrial dynamics revealed: “The level of GSH was also significantly improved and the level of lipid peroxidation was decreased significantly ( $p < 0.05$ ) by POLY-MVA.

The results indicate that POLY-MVA is effective to protect the age-linked decline of myocardial mitochondrial antioxidant status. The findings suggest the use of this formulation against myocardial aging.”

### **Alpha Lipoic Acid (ALA)**

ALA has been used for many years in various cancer therapies. In a 2012 paper<sup>xv</sup> the authors looked at neuroblastoma cells and potential for metabolic effect from both DCA and ALA. Their conclusions are revealing as to one potential mechanism by which ALA can have an anti-cancer effect: “These data suggests that LPA (ALA) can reduce (1) cell viability/proliferation, (2) uptake of [18F]-FDG and (3) lactate production and increase apoptosis in all investigated cell lines. In contrast, DCA was almost ineffective. In the mouse xenograft model with s.c. SkBr3 cells, daily treatment with LPA retarded tumor progression. Therefore, LPA seems to be a promising compound for cancer treatment.”

The question arises “why consider PolyMVA over ALA in a metabolic therapy?” In the past our experience was to use ALA with DCA as well as other support nutrients. This strategy was typically able to mitigate the DCA side effects. The down sides of the combination therapy however were that it required multiple supplements and in the IV form required slower dose escalation of ALA due to potential side effects. Additionally while ALA has some cancer metabolism effect based on the data presented elsewhere in this paper, and multiple patient responses, ALA did not have either the same level of synergy with DCA (as PolyMVA) nor the potential metabolic benefits of PolyMVA in combination with DCA. This led us to choose PolyMVA as the neuroprotective and mitochondrial agent over ALA and support nutrients.

### **Why combined therapies?**

The potential side effects of DCA (which can include neurological toxicity) and a deeper look into the mechanism by which DCA works led myself and Dr. Gurdev Parmar to postulate that Poly-MVA and DCA could have two areas of synergy if used together: One being a mutual anti-cancer benefit and the other to improve the safety and tolerance of the DCA. The first step after looking at the chemistry was to have a cell line study done to see if the synergy we saw “on paper” translated to cancer cell death. The short story is that both Poly-MVA and DCA had tumor kill but together they had additive benefit, and less DCA could be used with the same tumor kill.<sup>xvi</sup> This was the best of both worlds with regard to a potential synergistic combination.

As we all know what works on paper does not always work in the petri dish, and what works there doesn't always translate to animal or human use. Because of this I (from prior use of DCA and Poly-MVA) knew how to administer both agents safely so I knew that I could provide the therapy without any risk other than risks common to other IV therapies. I did however have to select a group of people with advanced cancer that had

failed all therapies (standard oncology therapies and natural therapies) and consented to this as a trial of unknown outcome (in oncology research a “salvage therapy trial”).

We began with a small group of patients, acquiring them one by one based on the above criteria, and over the course of two years implemented the therapy. The original case series is summarized in the table below and was part of the original study, but has not been published separately since reported (in the context of the whole trial outcomes) at the Society of Integrative Oncology.<sup>xvii</sup> For reference many times things discovered in studies take years to be published, if at all.

n = 9	Disease Progression	Stable Disease	Improved Quality of Life	Disease Regression
66 YO Male: NHL				XXX
5 YO Female: Mixed Acute Leukemia (MLL+)				XXX
71 YO Female: Multiple Myeloma				XXX
68 YO Female: Multiple Myeloma				XXX
72 YO Female: CLL			XXX	
65 YO Male: Metastatic Melanoma	XXX			
*Three Patients: GBM (high grade brain tumor) Post Surgery			XXX	

**A brief note about the above nine original cases:**

- Since this time there have been many others and I have seen similar positive results.
- Later additions such as HBOT, Exogenous Ketones etc. have only IMPROVED outcomes
- The ONE main discriminator of success above all others was ability to make the diet changes

## **Rationale:**

The basis of the therapy is outlined in the DCA and Poly-MVA sections above, but essentially the goal is to attack the cancer cell where it is weakest via its unique (but impaired) metabolism relative to normal human cells.<sup>xviiiixxxxxixxiixxiixxiv</sup> I and colleagues have used this therapy, and the newer versions of it, many times in the years since and have had similar results. Of course nothing works for everyone but this combination has certainly improved overall cancer outcomes in our clinical experience. It should be noted the original protocol involved dietary changes (to a low carbohydrate or ketogenic diet) and a small group of oral supplements.

It should be of significant note that the only difference in the “disease regression” group and the other groups in the table above was that the “disease regression” group were the most stringent on their diet changes. This became a reason to increase the focus on the dietary portion of the intervention in future patients.

I had never seen these results when using DCA alone so in my opinion the synergy seen is the petri dish worked in humans. Additionally the rate of side effects from the DCA were drastically reduced, such that nobody since has had to drop out of the therapy due to DCA related side effects. Overall this is one of the truly big advances in integrative cancer therapies in the past twenty years.

In moving this therapy forward I encountered the work Dominic D’Agostino (of the University Of South Florida School Of Medicine) was doing on metabolic oncology therapies in 2014 at the International Hyperbaric Medical Association.<sup>xxv</sup> His work with animals and mine in humans had many crossover points. The main addition when I looked at both protocols was to combine Hyperbaric Oxygen Therapy (HBOT) and exogenous ketones with my protocol.

Since 2014 we have treated many Stage-4 cancer patients with the combined metabolic therapy mentioned below. It has been safe and overall very effective in slowing disease, causing regression or stabilizing advanced cancer.

I believe based on the experiences of the past seven years with this evolving therapy that it holds a significant place as an effective intervention in advanced cancers. And while nothing certainly works universally in advanced cancer a combined metabolic protocol should be considered as a potential therapy in all cases.

## **PROTOCOL:**

Combined Metabolic Oncology Therapy – Protocol Overview:

Protocol Overview:

1. Dietary Intervention
2. Use of supplemental retinol
3. Use of intravenous Poly-MVA and DCA (Oral instructions follow)
4. Addition of hyperbaric oxygen therapy (HBOT)

Specific Protocol:

1. Dietary Intervention:

- Patients are on a ketogenic or (at least) low carbohydrate diet
  - When calculating carbohydrates use ONLY the “net carbohydrate” values (Net carbohydrate is [Total Carbohydrate – Fiber]). Ultimate ketone goal in blood is over 3.0 millimolar.
  - In either diet the patient needs to consume high fiber vegetables.
  - Most juices and smoothies have too much sugar and cannot be used.
- Oral ketone supplements starting at 2.5 grams BID and increasing to 5 grams BID as tolerated. [35 – 70 mg/Kg Pediatric dose BID]
- Daily intermittent fasting should be followed with the last meal ending at 7:00 PM and the first meal at 8:00 AM or after.
- If patients are losing weight / cachexic: Have them consume 10-20 mL of MCT [1-5 mL Pediatric] oil every 1 to 2 hours. They may need bile salts as support. Then look at their caloric macronutrient levels and adjust the fat up and potentially some increase in protein.
- Note that too high of protein will trigger glucogenic amino acid conversion and so this should be avoided.

2. Retinol Rx:

Patients are given Vitamin A: 25,000 IU Retinol [350 IU / Kg Pediatric] in a fat soluble (not carotenoid) form orally once daily.

If patient has AST/ALT over 300 decrease to 5000 IU daily.

3a. Administration of Poly-MVA and DCA intravenously as outlined below:

**The Poly-MVA IV is always first then the DCA IV follows directly after the Poly-MVA.**

The first IV is a test dose:

- Poly-MVA 10 mL in 500 mL Normal Saline [0.1 mL/Kg for Pediatric – in 100 mL NS] and then DCA 10 mg/kg in 500 mL Normal Saline [100 -250 mL in pediatric]
- Note: (For both above you may substitute 0.45 saline in dehydrated patients)

The following IV's are at full dose:

- **Poly-MVA** 25 mL in 500 mL Normal Saline [0.5 mL/Kg for Pediatric – in 100 mL NS] and then

**DCA** 20 mg/kg in 500 mL Normal Saline [100-250 mL Pediatric]

- Note: (For both above you may substitute 0.45 saline in dehydrated patients)
- In aggressive cases doses of Poly-MVA may be titrated up to 40 mL [0.5 mL/Kg] and DCA may be titrated up to 30-40 mg/kg – if tolerated.

3b. ORAL DOSING (see administration schedule below)

	<u>Day-1</u>	<u>Day-2</u>	<u>Day-3</u>	<u>Day-4</u>	<u>ALL DOSES BELOW ARE PER DOSE BID</u>
<b>Poly-MVA</b>	10 mL	15 mL	20 mL	20 mL	
<b>DCA</b>	5 mg/kg BID	7.5 mg/kg	10 mg/kg	10 mg/kg	

- These can be mixed together and consumed at the same time, twice a day. Most people find keeping them in the refrigerator is best (and they taste slightly better cold).

4. Use of concurrent HBOT:

- We begin with a 1.3 to 1.5 ATA trial, bottom time 60 minutes with O2 by mask. Dive may be increased to 1.5 ATA X 60 minutes. At higher ATA air breaks are required: Once at depth use O2 by mask X 15 min then 10 min air break then 15 min O2 by mask.
- SCHEDULE: Minutes 1-15 with mask; Minutes 15-25 without mask; minutes 25 to 40 with mask minutes 40 to 50 without mask and minutes 50-60 with mask.
- With the full protocol above TWO HBOT dives per week are optimal.

5. Lab testing:

- Baseline standard labs including Chemistries with eGFR and ALT, AST and CBC. Other labs as indicated for the patient.
- DRAW ALL FOLLOW UP **eGFR AND LIVER FUNCTIONS ON SUNDAY OR MONDAY AM BEFORE ANY IV'S ARE DONE**. If not the renal functions can be falsely altered.
- **If any neuropathy develops:** Stop the DCA for one to three weeks and reinstitute it at the test dose. Use additional PolyMVA and ALA along with other neurological repair supplements.
- **Note that with the synergy of the Poly and the DCA the DCA doses do not need to be as high as previously thought.**

#### 6. Duration and frequency of therapy:

- In the case series mentioned above, and patients since we have noted a variety of response patterns and a variety of treatment duration requirements.
- Frequency of treatment:
  - If using the **IV protocol** we administer the Poly-DCA twice to three times weekly
  - If using the **oral protocol** we have the patient administer the Poly-DCA 4 days weekly
  - **Supplements and diet changes are daily**, unless noted above
- Duration of treatment:
  - The first re-assessment is normally completed at 8 weeks unless there is an objective test (PET etc.) within 12 weeks and then it is extended to 12 weeks.
  - Assessment includes any disease specific markers, physical exam, general and quality of life symptoms, non-specific markers (e.g. HsCRP, LDH, AlkPhos etc.), imaging if indicated and any patient specific finding or marker indicated.
  - Re-assessment includes any pertinent positive findings in the above list.
  - If therapy is improving quality of life measures and or any of the above clinical markers we recommend continuing in one of the following ways:

- If disease is stable and clinical indicators dictate a maintenance schedule is designed. This is typically two to three days weekly oral Poly-DCA protocol with all supplements and diet changes continuing daily.
  - If improvements are positive but the underlying disease is aggressive we will recommend continuing the primary therapy schedule above and re-assessing in 8-12 weeks.
- Continued dietary alterations:
  - As the dietary alterations were key to success in the original case series of patient response we advise patients to continue the diet changes long term.
  - Same recommendation for the supplements.

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## Patient Handout

### Combined Metabolic Therapies:

### Metabolic Cancer Therapies – Dr. Paul Anderson

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The point of using a “metabolic” therapy protocol in cancer is to take advantage of the differences most cancer cells have from normal human cells. If this is done then the cancer cell is weakened while the normal cells are strengthened. This cannot be approached in a simplistic manner as metabolism is complex. For this reason Dr. Anderson, building on the work of many researchers, (13,14) has derived a comprehensive metabolic cancer therapy to maximize the potential benefits of such a therapeutic system.

Dr. Anderson has worked in cancer research and earlier had direct experience with these types of therapies. In 2009 as part of a “non-responder” arm of an NIH funded trial we (7) surmised a potential synergy of Diet changes, Dichloroacetate (DCA) + PolyMVA (LAMC) with Hyperbaric Oxygen (HBOT), Retinoids and exogenous ketones. A cell line study (1,8) with DCA and PolyMVA showed apoptotic cell synergy in GBM cells. Additionally chemically the two agents have a potential for physiologic mutual benefit in that typical DCA use requires cell protective support during treatment and LAMC has been shown to be neuroprotective and supportive to the mitochondrial complex. (2,3,4,5) The author had used DCA with supportive nutrients prior to this and abandoned its use due to a high side effect profile. Concurrent to the above we also began to add ketogenic and HBOT interventions as suggested in some data. (12)

In the original trial, using the principles of metabolic cancer therapy, we saw stable or regressed disease (cancer) in the majority of cases of non-responders. This led to the further investigation of this type of therapy in other patients with cancer.

Protocol as developed originally in the NIH funded trial in conjunction with Anderson Medical Specialty Associates / Advanced Medical Therapies can be found in the archived resources. (7,8,9) These protocols were effective but have been eclipsed by the more evolved protocols outlined below.

The evolved (modern) protocol in current use is explained below.

#### Protocol Overview:

1. Dietary Interventions:
  - Ketogenic or modified ketogenic diet
  - Clean sources of foods and liquids

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2. Use of supplements:
    - Particular forms of specific nutrients to enhance the metabolic therapy as assessed by your physician. This may include vitamins, minerals, fats, ketones or other supplements.
    - These may change based on diet changes and often are different based on tumor type.
  3. Use of either oral or intravenous PolyMVA and DCA
    - This is a crucial combination for both synergy as well as tolerability of therapy.
    - Neither works as well alone.
    - The pharmacological effect of the combination is to force the cancer cells into metabolism which weakens them.
    - At the same time normal cells are strengthened by the protocol.
  4. Addition of hyperbaric oxygen therapy (HBOT)
    - Increases delivery of therapies to the tumor areas
    - Lowers cancer triggering chemistry in tumors
    - Decreases side effects from other cancer therapies and improves quality of life

As a note, other therapies may be synergistic and your physician will assess these both in the beginning of therapy as well as during the process of your treatment protocol.

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