

Overcoming Chemotherapy Drug Resistance with Oxidizing Nutraceuticals: A Brief Review and Case Reports

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Abstract

Many stage III or IV carcinomas and lymphomas can be rendered into remission with standard-of-care chemotherapy protocols. Chemotherapy-induced cancer cell apoptosis is initiated by different primary intracellular toxic events, but all of these must ultimately culminate in mitochondrial outer membrane depolarization (MOMP). The final common pathway in most cases results from overwhelming intracellular hyper-oxidation. Unfortunately, many such cancers ultimately relapse, populated by chemotherapy resistant clones. Indeed, one of the most important mechanisms of chemotherapy resistance is amplification of the antioxidant capacity on the part of the resistant cells, such that standard dose chemotherapy by itself can no longer induce apoptosis. In order to overcome this barrier, pro-oxidant nutraceuticals were administered along with standard dose chemotherapy to suitable patients. All of the pro-oxidant compounds were given orally, and no measurable toxicity was observed. Illustrative case reports are presented, and a discussion of the potential for improving standard of care treatment of refractory cancers by this method is provided.

Keywords

Chemotherapy Resistance, Pro-Oxidant, Programmed Cell Death, Nutraceuticals

1. Introduction

Standard-of-care chemotherapy protocols that have been in use for decades are often capable of inducing complete clinical remission for many stage III or IV cancers, including aggressive malignancies, such as small cell lung cancer, ovarian

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cancer, invasive ductal breast cancer, inflammatory breast cancer, nodular and diffuse large cell lymphomas, Hodgkin's disease, multiple myeloma, colorectal cancer, gastroesophageal cancer *et al.* And yet, despite achieving an initial complete clinical remission, many such cancers will subsequently relapse, eventually causing the death of the patient. This is one of the great paradoxes in all of medicine. This article will explore some of the reasons that might explain this, as well as providing clinical and theoretical evidence for how to solve this crucial problem, which fundamentally limits the success of cancer chemotherapy.

Complete clinical remission typically equates to > 99% cell kill. A tumor measuring 2 cm in volume contains approximately 10 billion cells. Even after a 99.99% kill, the 0.01% remainder amounts to 1 million cells/2cc original tumor. The surviving cancer cells are by definition resistant, some by kinetics, some by sanctuary, but mostly by metabolism [1], so that when these cells repopulate, the original chemotherapy is no longer effective, because the cells that comprise a relapsed cancer are the progeny of a chemo-resistant clone or clones. To solve this problem, we need to take a closer look at the cancer cell's metabolic mechanisms of chemotherapy resistance.

The goal of chemotherapy is to selectively induce apoptosis in cancer cells. Historically that approach was to attack the DNA in the belief that the increased cellular proliferation rate of cancer cells would expose their DNA to chemical attack. This was a primitive but somewhat fortuitous concept, because it actually works, although not in the ways that were originally thought. In the 7th and 8th decades of the 20th Century when chemotherapy initially came into use, the precise mechanisms of apoptosis, AKA programmed cell death (PCD), were by no means understood. But now some 60 years later, the intrinsic pathway of PCD has been rigorously explicated.

Intrinsic pathway dynamics

The intrinsic pathway of PCD is the domain of the mitochondrion, the metabolic gatekeeper of the cell. There the bio-energetic center of cellular metabolism determines whether cellular function is adequate and thus worth maintaining. Conversely, when metabolism becomes inadequate or deleterious, mitochondria have the capacity to initiate the PCD pathway, resulting in cell death/apoptosis. In this way, one million cells in every adult, in every minute of every day, are rendered to apoptosis. This is how harmony amongst the 36 trillion cells is maintained, so that adult host can stay alive.

Research over the past several decades has taught us how mitochondria accomplish this. There is a huge body of literature available to the reader to explore this in greater depth [2]. For the sake of this discussion, it will suffice to describe the basics as follows: cellular metabolism requires oxidation of reduced organic compounds to release energy. While this process is extremely efficient, there still is waste product generated, referred to in general as reactive oxygen species (ROS), such as superoxide, hydrogen peroxide and hydroxyl radicals. In order for the cell to maintain a suitable redox milieu, antioxidants must be readily on hand to

quench the excess ROS. The most notable examples are super oxide dismutase (SOD), glutathione, NAD(P)H: quinone oxidoreductase 1 (NQO1), thioredoxin and catalase. But as the cell ages or deteriorates, these compensatory mechanisms can become insufficient. When the redox state gets far enough out of balance, the voltage that maintains the integrity of the mitochondrial membranes collapses, and the mitochondria releases cytochrome c, which activates the surrounding apoptosomes, which contain caspase. Upon their release, the caspase molecules then digest the cell. This is PCD [3].

Chemotherapy cell death mechanism revisited

Returning to chemotherapy and its ability to induce apoptosis, it has been adequately demonstrated that hyper-oxidation is the primary metabolic process involved. Arriving at this realization was a bit circuitous. Chemotherapy does largely attack DNA and not the mitochondria. But now we know that when DNA is damaged it is the mitochondria that must generate NADH and/or NAD(P)H to repair the DNA, and that providing the NADH NAD(P)H induces oxidative stress upon the mitochondrion [4]. Recall that the strategy behind chemotherapy has always been to exploit a fundamental metabolic difference between cancer and normal cells. And we recognize that because cancer cells are hyperproliferative, they require increased catabolism of reduced organic compounds, resulting in elevated levels of ROS [5]. It is for this very reason that cancer cells must contain much higher levels of antioxidant capacity than normal cells, in order to survive [6].

Returning to the issue of chemotherapy resistant cells, we can readily see that one of the main mechanisms of resistance is amplified antioxidant capacity. When chemotherapy induces DNA damage resulting in increased demand for mitochondrial NADH and NAD(P)H production, the resistant cells depend on their increased antioxidant capacity to neutralize the ROS so generated, in order to survive [7].

Possibilities for interfering with cancer cell chemo resistance

The question then becomes, “Is it possible to hinder the chemotherapy-resistant cell’s ability to survive the hyper-oxidative stress induced by chemotherapy, either by inhibiting cancer cell antioxidants or by administering pro-oxidant compounds concomitant with chemotherapy, in order to overwhelm the cell’s capacity to neutralize the ensuing hyper oxidative stress?”

In pursuit of answering this question, I report herein the clinical results of patients with chemotherapy resistant cancer who were treated with pro-oxidants and antioxidant-inhibiting compounds, given concomitantly with the chemotherapy to which they were resistant. The goal was to determine if the clinically demonstrated resistance to chemotherapy alone could be overcome, resulting in a clinical remission that was otherwise unobtainable by chemotherapy alone.

2. Materials and Methods

Patient inclusion criteria:

- 1) Demonstrated chemotherapy-refractory, clinically measurable malignancy.

2) Performance status > 80%.

3) Agreement to adhere to the requirements of the protocol and provide signed informed consent. All of the pro-oxidant supplements listed below are commercially available and/or nonproprietary, the treatment was considered simply integrative of homeopathic and allopathic standard-of-care treatments, thus not requiring IRB supervision.

Chemotherapy refractory malignancy in this study was defined as biopsy-proven, measurable cancer that had demonstrated lack of response to standard-of-care chemotherapeutic protocols. The patient was then instructed to take the oral pro-oxidant compounds as specified below, along with the same chemotherapy that they had previously failed, and to not take any other additional supplements. The goal was to demonstrate that the addition of the pro-oxidant protocol to the original chemotherapy regimen could restore its effectiveness.

Protocol compounds:

- 1) Beta-lapachone 200 mg
- 2) Vitamin C 6000 mg
- 3) Menadione 60 mg
- 4) Magnesium oxide 200 mg
- 5) Acetaminophen 1500 mg
- 6) Acetylsalicylic acid 975 mg
- 7) Sulindac 200 mg
- 8) Hydroxychloroquine 400 mg
- 9) Artemisinin 500 mg
- 10) Tributyrates 900 mg
- 11) Apigenin 100 mg
- 12) Luteolin 400 mg

These were taken either as 1 dose on the first day of each chemotherapy cycle, or the above doses were divided by half, taken on day 1 and day 2 of each chemotherapy cycle.

Case #1

58-year-old Caucasian female diagnosed with nasopharyngeal squamous cell carcinoma treated with cisplatin 5-FU chemotherapy by her local oncologist. After 3 months her tumor became refractory to treatment with enlarging disease on CT scan and increasing pain. But she otherwise had a good performance status. She was referred to me and she was given the above pro-oxidants along with the same chemotherapy regimen of cisplatin and 5-FU. After one cycle her pain was gone and after 2 cycles her CT scan showed no evidence of disease. She enjoyed a complete remission that lasted for more than 2 years. Because she was one of the very first patients on this protocol, she did not receive beta lapachone, hydroxychloroquine or tributyrates because they were not initially available to me. Further case studies revealed that the squamous cell carcinomas of all varieties demonstrated exquisite sensitivity to this protocol and typically did not require all of the supplements listed above

Case #2

55-year-old Caucasian woman with extranodal large cell lymphoma of the breast treated aggressively with R-CHOP. Initial response was incomplete despite repeated cycles. The above protocol supplements were then administered, absent hydroxychloroquine tributyrate and hydroxychloroquine. The patient's residual refractory breast mass completely resolved and she enjoyed a sustained complete remission and was ultimately cured without further treatment. She did not have metastatic disease and her disease was fully measurable by breast MRI.

Case #3

44-year-old Hispanic male with stage III Hodgkin's disease treated with ABVD with only partial response and very poor tolerance. He refused to continue full dose chemotherapy and was referred to me for an integrative approach. At his insistence he was given the above protocol supplements absent hydroxychloroquine, with just 40% doses of Adriamycin and dexamethasone and no other chemotherapy. He was able to work full-time as a construction contractor during the treatment with essentially no significant nausea vomiting or myelosuppression. He rapidly went into complete remission and has been free of disease now for 5 years. His disease was initially palpable and easily measurable by exam and PET scan.

Case #4

24-year-old Caucasian female with nodular sclerosing Hodgkin's disease. Her father was a CEO of an offshore integrative oncology research program. She was treated there without success and then treated at Burzynski without success. She came to our clinic with massive disease in her neck and mediastinum compressing her airway, on the verge of respiratory distress. Only then was she agreeable to taking any chemotherapy. She agreed to 80% doses of ABVD x 2 cycles only, along with the above protocol absent hydroxychloroquine which was not part of my protocol at the time. Despite having massive stage IV disease at the onset, shortly after starting treatment her disease began to disappear, leading shortly thereafter to complete remission. She continued to menstruate throughout the chemotherapy. She went on to get married and have 2 children requiring no fertility enhancement, and is cured of her disease. Although she is not likely the others a case of failing initial standard of care chemotherapy, the degree and duration of her response despite receiving a very small fraction of the standard of care chemotherapy dosing is quite noteworthy with respect to the hypothesis that the supplements enhance chemotherapy effectiveness.

Case #5

65-year-old Caucasian male with colorectal cancer presenting with liver metastases treated with FOLFOX/Avastin achieving only a partial response, and without further response despite subsequent intensive dosing. Disease was readily measurable with CEA and CT scans and PET scans. He was then given the pro-oxidant protocol just 1 time, along with the same chemotherapy, and achieved a complete remission. He refused further treatment until relapsing 10 months later. He is now being rechallenged because he only received 1 cycle of the protocol plus chemo.

He experienced less nausea vomiting and diarrhea while taking the supplements compared to his pre-protocol experience.

Case #6

55-year-old Caucasian woman with stage IV colorectal cancer metastatic to her liver treated with FOLFOX and Avastin, only achieving a partial response despite 6 months of intensive therapy. Her liver metastases did resolve with initial treatment but her residual primary had to be resected showing quite a bit of aggressive disease. She relapsed 1 year later treated again with FOLFOX Avastin and had no response. She was then treated with protocol supplements above and achieved a complete remission. One year later she relapsed and went again through the same process and again achieved a complete remission. She has now been off of all treatment for almost 1 year with very stable minimal residual indolent disease and normal performance status. As with the other cases, nausea and vomiting and myelosuppression were reduced compared to their pre-protocol treatment experience.

3. Discussion

From its inception some sixty years ago, the chemotherapeutic treatment of malignancy has resulted in both the encouraging success of inducing clinical remissions, but also the discouraging outcome of relapsing refractory disease. Medical oncology research efforts have mostly focused on overcoming disease relapse by the administration of more complex protocols, or regimens of higher dose intensity. These efforts have been largely unrewarding. While there is a substantial body of research regarding the resistance mechanisms of cancer cells to chemotherapy, there has not been a concomitant research effort to directly overcome these mechanisms. This is somewhat difficult to understand because the mechanisms of chemotherapy drug resistance are to a reasonable extent well elucidated. The primary mechanism as described above is amplification of antioxidant capacity on the part of the cancer cell, thus allowing it to withstand the hyper-oxidative effect of chemotherapy.

The compounds above were chosen for their inherent pro-oxidant capacity or their ability to inhibit cellular antioxidants. Beta lapachone is a demonstrated potent inhibitor of one of the key cellular antioxidants previously mentioned: NQO1 [8]. Vitamin C in combination with menadione has potent antioxidant activity, in particular also as an inhibitor of NQO1 [9]. Apigenin and Luteolin modulate Nrf2 [10]. The Nrf2 pathway is a critical cellular defense mechanism that regulates antioxidant responses and detoxification processes, playing a significant role in protecting against oxidative stress. Nrf2 is typically upregulated in the malignant state [11] [12]. While Apigenin and Luteolin may enhance Nrf2 activity in normal tissue, their effect within the hyper-oxidative milieu of the cancer cell is reportedly quite different [13].

Sulindac inhibits surviving and reportedly also AMPK [14] [15]. AMPK plays a crucial role in regulating antioxidant defense during oxidative stress by upregulating several antioxidant gene products such as SOD and thioredoxin. AMPK can

also potentially upregulate Nrf2 [16]. Sulindac can also increase cellular oxidative stress by inhibiting NF-kappaB-mediated signals [17].

Another very remarkable observation in this study was the absence of any discernible toxicity by use of the supplements, along with a decrease in the typical chemotherapy toxicity that the patients had previously experienced with chemotherapy alone. This is not surprising because the redox state in normal cells is quiescent, so that a small uptick in intracellular oxidation would seem to have no noticeable effect. But the redox state within a cancer cell is typically on the edge of PCD [5], so that these compounds taken orally were able to achieve the intended effect: exceed the tolerance of the mitochondrial transmembrane voltage potential (TMVP), thereby inducing mitochondrial outer membrane depolarization (MOMP), thereby initiating the PCD cascade.

Further research suggested by these results would include use of autophagy inhibitors such as mebendazole or ivermectin, or additional pro-oxidants such as copper, sulfasalazine ciprofloxacin disulfiram etc.

One of the remaining obstacles in the pro-oxidant approach to treating chemotherapy resistant cells is the inhibition of catalase. Catalase is present in virtually all organisms exposed to oxygen, and is the main reducing agent of hydrogen peroxide. Aminotriazole as an herbicide had been used as a catalase inhibitor for decades but is not available for human use. Further research on safe and effective catalase inhibitors is underway, and progress thereto could potentially be of great benefit in this approach to treating chemotherapy resistant cancer [18].

4. Conclusions

These case reports suggest a potential breakthrough in cancer chemotherapy. Overcoming chemotherapy drug resistance in otherwise refractory advanced malignancy has been a goal not previously reported to date. Abrogating chemotherapy drug resistance by administering pro-oxidant nutraceuticals and inhibitors of antioxidants, as a means to enhance chemotherapy cytotoxicity, was shown to be feasible, well-tolerated and capable of converting lethal disease into remission status. In an exploratory study such as this, the primary goal was to demonstrate proof of concept. I believe these cases do just that. To my knowledge, this is the first such report of clinical results successfully utilizing this approach.

Finally, a cautionary note is in order. Increasing ROS is one of the hallmarks of cancer, and as described above can potentially be exploited to improve the therapeutic index of chemotherapy. But in certain circumstances, ROS amplification can actually increase proliferation and metastasis [19]. The cases presented here are the outcome of over 8 years of painstaking judicious clinical investigation. Further translational research from apothecary to clinic in this arena, is necessary to more precisely determine the optimal interventional strategy.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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