

Chapter 38
**An Innovative, Integrative Treatment Protocol:
The Individuality of Cancer and Cancer Treatment**

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ABSTRACT

The incidence of cancer continues to rise at alarming rates in most westernized nations. Yet our management of advanced stage cancer is little more effective than it was twenty years ago. This article reviews the failures of current clinical approaches to cancer, and introduces an innovative, integrative treatment protocol that takes into consideration the individuality of cancer and its treatment.

INTRODUCTION

The incidence of cancer continues to rise at alarming rates in most westernized nations. Yet our management of advanced stage cancer is little more effective than it was twenty years ago. The purpose of this article is to elucidate why the current paradigm of research and treatment is ineffective for advanced malignancy. In this article, I present a promising cancer protocol that integrates targeted chemotherapy, off-label use of pharmaceutical drugs, and natural supplements.

FAILURES OF CURRENT APPROACHES TO CANCER

While cancer research forges ahead, leading to new drugs for various malignancies, the efficacy of the vast majority of drugs has been disappointing. Are our models through which we research cancer in the laboratory valid? It is not uncommon for new anti-cancer drugs or therapies to show highly effective, and sometimes even spectacular anti-cancer treatment results using transplantable tumors in mice. These models frequently involve human tumor xenografts grown subcutaneously in immune deficient hosts such as athymic (nude) or severe combined immune deficient (SCID) mice. Unfortunately, such preclinical results are often followed by failure of the drug/therapy in clinical trials. On the other hand, if the drug is successful, it usually has only modest efficacy results. Why don't our successful animal results translate to successful human results? The typical xenograft model rarely causes lymphatic and/or vascular invasion, metastases, and death. This method does not represent clinical cancer in the human. In other words, cancer cells from a human, which are then grown in vitro, do not behave like human cancer when transplanted to an animal.

Not surprisingly, this has provoked considerable skepticism about the value of using such preclinical models for early stage in vivo preclinical drug testing. As a result, a shift has occurred towards developing and using spontaneous mouse tumors arising in transgenic and/or knockout mice engineered to recapitulate various genetic alterations thought to be causative of specific types of respective human cancers. Alternatively, the opinion has been expressed of the need to refine and improve the human tumor xenograft models, e.g., by use of orthotopic transplantation (directly from a human) and therefore promotion of metastatic spread of the resultant "primary" tumors. It has been demonstrated in over 70 publications describing 10 tumor types that orthotopic transplantation allows the growth and metastatic potential of the transplanted tumors to be expressed and truly reflects clinical cancer in the human. Unfortunately, the majority of cancer scientists are still using the traditional xenograft model, which may explain the dismal clinical predictions of our animal studies.

I would be remiss if I did not mention the drastic increased incidence of breast cancer, coupled with a lack of efficacious treatments. An interesting, but disappointing article was published in *The Scientist* on September 16, 2008. The following summary of this article may explain, at least in part, our failure to improve breast cancer treatment: Cancer cells taken from tumors and grown in the laboratory are the mainstay of cancer research, and are used as the model for studying tumor behavior and response to treatment. For the past 25 years, most of the laboratory research into metastatic breast cancer has been based on a single breast tumor cell line known as MDA-MB-435. At least 650 papers have been published on studies involving this cell line. Yet it has been revealed that this supposed breast cancer cell line may in fact not be composed of breast cancer cells at all. Instead, it appears that the cells are derived from melanoma. For 25 years, therefore, breast cancer research using MDA-MB-435, which is one of the most widely used "breast cancer" cell lines, has been based on an incorrect model.

Melanoma-derived tumor cells are not biologically equivalent to breast cancer cells; they have different molecular and genetic characteristics.

A study published in *Clinical Oncology* in December 2004 recapitulated our obvious failure in our attempts to treat malignancy. The study, titled “The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies,” analyzed the results of randomized clinical trials completed from 1990 to 2004, performed in the U.S. and Australia. It reported a statistically significant increase in 5-year survival due to use of chemotherapy in adult malignancies, finding that the contribution to 5-year survival in Australia was 2.3%, while in the U.S. it was 2.1%. The study also reported that the median survival in lung cancer has increased by 2 months in the past 20 years. Further, overall survival benefit of less than 5% has been achieved in the adjuvant treatment of breast, colon, and head and neck cancers. The researchers also did find that chemotherapy significantly extended 5-year survival in testicular cancer (41%), Hodgkin’s Disease (38%), Non-Hodgkin’s lymphoma (10.5%), and Ovarian cancer (8.8%).

The reasons for the inadequacy of chemotherapy are multiple and complex, the details of which are beyond the scope of this article. Table 1 presents the leading ten factors that are responsible for the relative ineffectiveness of chemotherapy.

RANK	FACTOR	EXPLANATION
1	Cancer Cell DNA Mutation	Cancer cells experience rapid turnover and thus mutate at a much greater rate than normal cells. In addition, chemotherapeutic regimens force mutations by enhancing natural selection of the cells that are resistant to the therapy to which they are exposed.
2	Gene Amplification	Cancer cells have the ability to up-regulate production of specific proteins and/or receptors which confers resistance to certain chemotherapy regimens.
3	Drug-pumping Mechanisms	Cancer cells may develop proteins that pump chemotherapy out of the intracellular space and back into the interstitium.
4	Repairing DNA Breaks	Many cancer cells develop the ability to repair their own DNA.
5	Cancer Stem Cells	Cancer stem cells appear to be much more resistant to chemotherapy than the bulk of the differentiated mass.
6	Inactivation of Drug	Cancer cells may develop mechanisms to inactivate chemotherapy drugs.
7	Extracellular Tumor Environment	Cancer cells pump hydrogen ions out of the cell; this acidifies the extracellular environment, which will often inactivate chemotherapy, while promoting angiogenesis.
8	Poor Tumor Blood Supply	Most tumors have regions that are poorly perfused with blood. This limits the amount of chemotherapy that can reach the tumor, while promoting hypoxia; hypoxia promotes angiogenesis.
9	Cancer Involves a Multitude of Mechanisms	Cancer progresses through a multitude of mechanisms, while chemotherapy targets only a few.
10	One Size Fits All	Most patients with the same type of tumor begin their chemotherapy using the same drug regimen. Yet, every tumor has a unique genetic profile, which constantly mutates; some patients will respond to a given regimen while some will not.

Table 1. Top Ten Factors Contributing to the Relative Ineffectiveness of Chemotherapy

Most patients with the same type of tumor begin their chemotherapy using the same drug regimen. For example, a patient with non-small cell lung cancer typically receives a taxane and a platinum, with or without bevacizumab. The problem: every tumor has a unique genetic profile, which constantly mutates; some patients will respond to this regimen and some will not. Is there a way to tailor the regimen to each individual’s cancer?

The pharmaceutical model of “one size fits all” works well for many other disorders such as hypertension, diabetes, and high cholesterol. Regardless of the cause of hypertension, if you give a drug that relaxes the vessel, hypertension is controlled. Regardless of the cause of diabetes, if you increase insulin receptor sensitivity, or replace insulin (for type I diabetes), you control blood glucose. The same drug can work for all.

A NEW APPROACH TO CANCER

Cancer is a different disease in each individual, and it is a constantly mutating disease in each individual. Therefore, each patient must be treated based on the genetics of their primary tumor and their circulating tumor cells. When tissue is obtainable, the molecular markers (e.g. MDR or VEGF expression) of the tumor can guide chemotherapy. When a patient presents with progressive metastatic disease, despite chemotherapy, it indicates that the tumor is resistant to that specific chemotherapy. To determine which chemotherapy should be used next, one should collect the circulating tumor cells (CTC) from the blood. These cells, which are of epithelial origin (and therefore easily separated out from blood cells) may be tested for expression of various receptors and genetic mutations using reverse transcriptase PCR. It then becomes clear which chemotherapy would be more likely to be effective, and which would be unlikely to be effective. If the patient responds with a temporary remission, but then relapses, the physician must once again collect the CTCs, which should reveal evidence of mutation.

THE FUTURE OF CANCER THERAPIES

At the present time, comprehensive molecular assays of circulating tumor cells are not commercially available in the U.S. However, those assays are available in Germany and they will accept blood samples from all countries. This is, indeed, the future of chemotherapy; treating each cancer only after the genetic and molecular characteristics are determined.

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