



Chemosensitivity Testing – Customizing Cancer Treatment

By Mary Budinger

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There is a struggle in oncology over the use of chemosensitivity and chemo-resistance testing: can these tests produce better outcomes for patients?

If a patient presents with a bladder infection, for example, it is routine to send a sample to the lab and test it with the various antibiotics available to see which is most effective because results vary, depending upon the individual person. But it is not routine to test a sample from a cancer patient to determine which chemotherapy drugs would be most effective.

Most patients are subjected to a one-size-fits-all approach to chemotherapy. For instance, the drug trio of Adriamycin®, Cytoxan®, and Taxol (ACT) is a standard chemotherapy protocol given to many breast cancer patients. But a landmark study published 2007 in the *New England Journal of Medicine* found that Taxol does not work for the most common form of breast cancer – when the genetic marker is HER2 negative and the tumor is estrogen receptor positive (meaning estrogen helps it grow).¹ Some 80 percent of breast cancer patients are HER2 negative and that prompted oncologist Anne Moore, M.D., Professor of Clinical Medicine at the Weill Medical College of Cornell University in New York to editorialize, "The days of 'one size fits all' therapy for patients with breast cancer are coming to an end."²

Given that chemotherapy drugs have considerable toxicity associated with their use, a one-size-fits-all approach runs afoul of the famous Hippocrates admonition that physicians should do no harm.

The concept of not doing harm was the focus of the Best Answer for Cancer's 11th Annual International IPT/IPTLD Integrative Cancer Care conference last April in Dallas, Texas. Chemosensitivity tests were a significant part of the discussion because they open the door to a more personalized approach to cancer treatment.

"We are at a crossroads, and need to take a different way to approach cancer patients," Ioannis Papisotiriou, M.D., Ph.D., of Greece told attendees. He is the medical geneticist who established Research Genetic Cancer Center (RGCC), Ltd., in Greece to perform chemosensitivity tests.

“We need a more personalized approach, we need more data about how effective the natural and chemical substances can be, and we need to use this information not only with proliferate cancer cells, but also the cancer stem cells that may stay in a dormant state.”

The RGCC test – what doctors call the “Greek Test” – uses blood preferably, and tissue when necessary, to identify circulating tumor cells (CTCs) and cancer stem cells (CSCs). This particular assay tests 49 chemo drugs in 5 classes, plus 64 tumor related genes looking for mutation, and 50 natural biologics.

The list of biologics includes Nrf2 Activator, Artecina, Proteo-Xyme, Arabinogalactan, Aromatase Inhibitor, Dextrol, Cellular Vitality, Epimune Complex, Cat’s Claw Forte, Retenzyme Forte, metformin, Salicin, Mammary PMG, quercetin, Super Artemisinin, Oncoplex ES, Poly-MVA, C-statin, ascorbic acid, Superoxide Dismutase, Ukrain, Bio-Ae-Mulsion Forte, Bio-D-Mulsion, NuMedica Micellized D3, curcumin, Vitinox, mistletoe, AHCC (Active Hexose Correlated Compound), Amygdalin (B17), Thymex, burdock complex, Salvestrol, Virxcan, Immune Plus (fermented soy extract), DCA (dichloroacetate), genistein, PME, new PME, OPC, Intenzyme Forte, Cruciferous, CV247, lycopene, green tea extract, paw-paw, Indol-3- carbinol, melatonin, Naltrexone, resveratrol, and oleander extract.

James Forsythe, M.D., HMD, of Nevada embraced chemosensitivity testing about 3 years ago because he had become disheartened with the results he was getting with conventional oncology. Chemosensitivity testing is now a cornerstone of his protocol. He uses the RGCC test.

“I can see the efficacy of all the drugs and supplements tested and I take the best,” he said. “The report comes back in 10 days to 2 weeks, and patients feel empowered because they have a blueprint. I don’t believe you can administer chemotherapy – even the low dose insulin potentiation therapy (IPTLD) which I use – without a test. When I look at the test results for the drugs, I look for the high responders, those that achieve about 80 percent sensitivity. We do not use drugs that we think will be less than 50 percent effective. With the supplements, the percentage does not have to be that high because so many of them are helpful in going after the cancer stem cells and boosting the immune system.”

Dr. Forsythe is a member of the International Organization of Integrative Cancer Physicians (IOICP) and sits on the Board of Directors of the Best Answer for Cancer Foundation. He and many of his colleagues use insulin as a biological response modifier to briefly rob cancer cells of sugar, their primary fuel. When a patient’s blood sugar level drops to about the low 40s, IPTLD practitioners generally administer about one-tenth the conventional dose of chemotherapy. IOICP physicians are able to target cancer cells, and avoid significant damage to healthy cells. Adding chemosensitivity testing to the protocol allows them to choose drugs that should have more efficacy than others, thus sparing patients further harm.

Dr. Forsythe is conducting a 5-year outcome study of his cancer protocol which involves the use of IPTLD with chemosensitivity testing, his own custom immune therapy, and PolyMVA. At the conference, he reported on his results.

“After 33 months, with 450 stage IV adult cancer patients, we have a phenomenal survivorship rate of 59%,” he said. “There is no more definitive answer to those who question your modality than outcome studies. There are no two clinics who do IPTLD exactly the same way – we all tweak it a bit – but the one variable you do not change is whether the patient is still alive after 5 years.”

At the conference, Dr. Papisotiriou explained that he prefers working with blood samples in the lab, rather than tissue because:

- CTCs are the progenitors of every micro-colonization; it is appropriate to analyze relevant cells related to the process of metastases.
- To isolate the cancer cells from a tissue sample, requires multiple and long periods of cultivation processes which will force changes to cancer phenotype and genotype.
- The gene expression analysis may not always relate strongly with the phenotype and this may cause false positive or false negative assumptions during the analysis only using one or the other method.

“RGCC labs adds one final step not used by any other labs that we know of at this time,” Dr. Papisotiriou explained. “This final step is verification of the genetic findings. This means we actually test each patient’s CTCs and CSCs independently against each chemotherapeutic agent and natural substance on the list. This ex-vivo type testing is accomplished by expanding the few CTCs and CSCs harvested from each patient by using his world/international patent cell culture. This culture removes the Hayflick limit [the number of times a normal cell population will divide until cell division stops] of these cancer cells and allows them to multiply at a phenomenal rate, creating many billions to trillions of identical CTCs/CSCs with no change to their genetics, epigenetics, and phenotype expressions. By using powerful sorters and flow cytometers as well as negative selection based interrogation, we are able to actually isolate the relevant CTCs and not enrich them. Hence, we manage to have a pure sample of CTCs and simultaneously harvest all the subset of CTCs from a single blood sample. So what we are working with is identical to the original harvested cells from the patient.”

Ray Hammon, D.C., N.D., of Texas runs the United States branch (RGCC-USA, LLC) of the RGCC, Ltd., Greece Lab. He does not see the benefit of using cell lines to develop a personalized patient-centered cancer care program.

“Laboratory cell lines can and do become contaminated,” he said. “They have taught us a lot and yet I feel they are a deeply flawed tool for teaching us how to treat patients clinically. This is

why a very small number of drugs developed this way ever make it to being truly effective in inducing apoptosis of cancer cells in vivo. The cell lines are often much more sensitive to everything that is tested against these cells. To create an individual therapy based on these cell lines is very hard to do.”

There are about a dozen labs which do chemosensitivity testing; some are in Europe and some are in the United States. Some use just tissue, or just blood, or both. Some give a simple list of recommended drugs to use based on cellular genetics only; some give more information.

Chemosensitivity testing has been used since the mid-1990s. It has been opposed by many insurance companies and by the American Society of Clinical Oncology (ASCO) because there have been no prospective, randomized trials to provide evidence that patients who were treated based on a test performed better than the traditional one-size-fits-all chemotherapy.

A 2004 study conducted by an ASCO Working Group found that the evidence base for recommending chemosensitivity testing in routine clinical practice is lacking.³

Robert A. Nagourney, MD, Medical and Laboratory Director of Rational Therapeutics, Inc., of Long Beach, CA, questioned the criteria used by the ASCO Working Group at the time, the composition of the Working Group itself, and the fundamental definition of a chemosensitivity and resistance assay that they employed.

“In the 2013 ASCO proceedings (Apfel, C, et al Proc ASCO, 2013, abst. 22188), our meta-analysis demonstrates a greater than 2-fold improvement in response among patients where assay therapy was used,” Dr. Nagourney said.

In his lab, he tests the tumor in its native state: tissue.

“I have scientific misgivings about a test that isolates a cancer cell from its environment and begins to measure it and probe it, because very few cancers reflect discrete genetic events,” Dr. Nagourney clarified. “There is no cancer patient who has been diagnosed on a CTC; they are diagnosed on tissue. Cancer is not simply a genetic disease. I think cancer is a system that harmonically oscillates between the cancer cell and its microenvironment. Without the microenvironment – tissue – you don’t have a good handle on the environment – vascular, stroma, B-cells, T-cells, macrophages, cytokines, and tumor cell to tumor cell communication. I think you need to look at the whole entity, not just the tail of the elephant. But if grabbing the tail of the elephant helps you, then use it. All assays that can be shown to help achieve better outcomes for patients should be used.”

Because prospective, randomized, controlled clinical trials cost millions of dollars, people are reluctant to invest that much money for something difficult to patent. That said, the 2011 edition of the oncology textbook, *Cancer: Cancer Principles and Practice of Oncology: Primer of the*

Molecular Biology of Cancer, recognizes the value of using an assay to identify cancer stem cells:

Evidence for the existence of biologically distinct CSCs [cancer stem cells], first demonstrated in a hematological malignancy and in the past 5 years in several solid tumors, has shaped a new paradigm of human cancer as a hierarchical disease whose growth is sustained by a population of CSCs. This conceptual shift has important implications not only for researchers seeking to understand mechanisms of tumor initiation and progression, but also for the development and evaluation of effective anticancer therapies.

Thus, research must be directed at the relevant cell populations as identified through functional assays, the ultimate goal being the rational development of therapies that interfere with the oncogenic program within the CSCs.

The CSC model postulates that with an appropriate purification strategy, the CSCs with the capacity to initiate and sustain tumor growth *in vivo* can be identified and isolated from the bulk cells that do not have tumor-initiating activity.⁴

Sean Devlin, D.O., M.D.(H), HMD, of Nevada is a certified IOICP instructor for the use of insulin potentiation therapy. He sits on the Medical Advisory Board for the Best Answer for Cancer Foundation. He has used several different labs, both in Europe and in the United States.

“I’ve taken blood from the same patient, drawn at the same time, and sent it to labs in Europe and in the U.S.,” he said. “The American lab would say zero circulating tumor cells were found but the European tests found them. So it casts doubt both ways. Tissue has a little of the infrastructure still there so, based on literature, there may be more reliability. With blood, you have captured a little of the free cells in circulation that have escaped the tumor and are growing. It depends upon what you are looking for. Anytime you take a cell and expose it to growth factors, you are changing those cells. We are talking about taking cells in cultured medium – *in vitro* – and that is not how the body works.”

Dr. Devlin uses chemosensitivity testing in his practice, even though he describes the effort as still in its infancy.

“I think the testing should be done, but the accuracy of the testing is not 100 percent every time. Yet, that is true of many things in medicine. I think the real issue is that although there is no gold standard for chemosensitivity testing at this time, it is beckoning the call for more personalized care. There is no one recipe for every cancer patient. If we can provide individualized and better outcomes with chemosensitivity tests, more power to us. This is a stepping stone to get to where we want to be: providing individualized cancer care for patients.”

*Mary Budinger is an Emmy award-winning journalist who writes about integrative medicine.
She can be reached at 602-494-1999.*

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(see below for photo options and footnotes)

PHOTO OPTIONS



James Forsythe, MD, HMD, updating his outcome-based study of 450 adult stage IV cancer patients after 33 months. Chemosensitivity testing is part of his protocol.



James W.
Forsythe, MD,
HMD, of Reno,
Nevada



Ray Hammon,
DC, ND, of
Rowlett, Texas



Ioannis
Papatotiriou,
MD, PhD, of
Filotas, Greece

¹ Hayes DR, Thor AD et al. *N Engl J Med*. October 11, 2007; 357:1496-1506. DOI: 10.1056/NEJMoa071167

² Moore A. [Breast-Cancer Therapy - Looking Back to the Future](#). *N Engl J Med*. October 11, 2007; 357:1547-1549. DOI: 10.1056/NEJMe078153

³ Goodman A. [Chemotherapy Sensitivity - Resistance Assays: ASCO Assessment Says Not Enough Evidence to Support Use](#). *Oncology Times*. [October 2004 Vol 26 :19, p 10-16](#) doi: 10.1097/01.COT.0000292338.52364.7c

⁴ DeVita Jr., V., Lawrence TS, Rosenberg SA. *Cancer: Principles & Practice of Oncology: Primer of the Molecular Biology of Cancer*, Philadelphia, PA: Lippincott Williams & Wilkins; 1 Pap/Psc edition 2011.