

CHAPTER FIFTEEN CHEMOTHERAPY

**Drs. E. David Crawford, Aubrey Pilgrim, Stephen Strum, Israel Barken,
Bob Leibowitz and Contributions from Several Survivors**

Introduction

Chemotherapy is the use of drugs that hopefully will kill more cancer cells than normal cells. It is used primarily for advanced metastatic disease. This is a chapter that is challenging to write because until recently there were very few positive chemotherapy drugs and treatments that we could write about. This is not to say that you should be discouraged and give up hope. There is hope and there are many new drugs and protocols that are being investigated. Just hang in there.

We mentioned it before, but if you do not have a computer, by any and all means, get one. It can help you enormously. Computers are fairly inexpensive today. Even if you have to give up going to the opera a couple of times, or out to a fancy dinner every other night, use the money to buy a computer. There are thousands and thousands of web sites that offer tons of information. Use the computer to search the websites. You can use www.yahoo.com, www.excite.com, www.lycos.com or any of several other search engines. Then type in whatever you want to search for and you will be amazed at the number of sites that have the information you are seeking. Much of the information is revised and updated often.

Prostate Cancer and Breast Cancer

You can search the Internet for prostate cancer and will see many sites, but if you search for breast cancer you will be presented with about ten times as many as for prostate cancer. You can search for prostate cancer AND chemotherapy and you will see very few sites. Do the same for breast cancer AND chemotherapy and again, you will see about ten times more sites.

You will also see that the chemotherapy for breast cancer has more positive results than treatments for prostate cancer. Fortunately, many of the chemotherapy drugs used for breast cancer can also be used for prostate cancer. Unfortunately, they don't always work as well on men as on women.

One of the reasons we see so much more about breast cancer is because they have raised much more money for more research. We men should be ashamed of ourselves because we have not done more to help ourselves.

Hormone Refractory PC (HRPC)

Co-author E. David Crawford, writing in UROLOGY 54-51-52 1999, has an optimistic view of successful HRPC treatments:

"Although severing the grip of hormone refractory prostate cancer (HRPC) still eludes us, there is reason to be optimistic that we may soon witness a change. Several chemotherapeutic and biologic agents (taxanes, estramustine, antisense oligonucleotides) have been evaluated in phase I and phase II clinical trials with encouraging outcomes; phase III trials are currently being developed. A phase III trial of the chemotherapeutic regimen of combined mitoxantrone and prednisone has shown improvements in outcomes.

More importantly, however, are the cases of complete or partial response that are being observed with these newer treatments. Data emerging for the taxanes, alone and in combination with estramustine, have renewed interest in chemotherapy for HRPC. Equally promising is the confirmation that newly recognized cellular mechanisms may represent exploitable vulnerabilities in the disease process.

A rationale for early treatment is that within prostatic tumor masses, as with many other cancers, genetic heterogeneity of the malignant cells increases with tumor enlargement. This heterogeneity makes it less likely that any form of treatment can affect a durable response. Thus, controlling cellular proliferation with earlier treatment might minimize the appearance of genetic diversity within tumors."

You have seen the word heterogeneity mentioned several times. Heterogeneity means that several different cells appear such as those which become hormone independent. Homogeneity would mean that the cells are all the same.

The treatments that we have for early stage prostate cancer, in the majority of cases, may either cure it or hold it in check for several years. But in some cases, in spite of all we do, the cancer may break through and the PSA will start to rise. Combined Hormone Therapy (CHT) is usually our first line of defense after a surgical or radiation treatment failure. The CHT may work for sometime, but some patients eventually develop hormone refractory prostate cancer (HRPC). HRPC may also be called Androgen Independent PC (AIPC). Advanced PC may not be the same thing. Advanced PC can be cancer that is outside the prostate, but it may still be responding to CHT.

We don't know why some men become refractory to CHT. Some believe that there are hormone independent cells from the very beginning of the cancer. When the patient then goes on hormone therapy, the dependent cells are

killed off, leaving only the cells that do not depend on hormones to survive and proliferate. It is these hormone independent cells are that eventually kills the patient.

Others believe that the hormone independent cells are due to cell mutations while on hormone therapy. They believe that the longer one waits before going on hormone therapy, the longer he has freedom from the AIPC. No one knows for sure what the answer is. Some very prominent doctors recommend that hormone therapy should not begin until there are symptoms. Symptoms are usually due to bone pain. At this stage, usually there is widespread metastases.

When to Start Treatment

Logically, it would seem that the sooner one began treatment with hormones, the less tumor burden and the more control that can be exerted. We believe that CHT should be instituted early and so do a lot of other doctors.

When the PSA continues to rise and no longer responds to maximum androgen blockade (MAB) or CHT, there are several chemotherapeutic drugs and protocols that can be instituted. The taxanes, paclitaxel and docetaxel seem to offer a lot of hope. Taxol and taxotere are the active ingredients in these drugs. They have worked very well for breast cancer.

Harry Pinchot a HRPC Survivor

Harry Pinchot is an example of a survivor with HRPC. He is a young man who became hormone refractory and had some chemo treatments. He was 54 years old on 9/21/94 when he had his first PSA of 16.9 and a negative biopsy. On March 30, 1995 his PSA was 31.2 and another biopsy confirmed cancer. He began CHT but his PSA never went to undetectable. It went to its lowest on 8/02/95 when his PSA was 0.2 using the Immulite ultra sensitive test. He decided to go on injections of Velban, oral Emcyt and radiation. His PSA went down to .01 on 9/26/95. He stopped his CHT. But then seven months later, the PSA started creeping up again.

On 5/09/96 his PSA was 3.17. He resumed CHT and added thalidomide to his regimen. On 11/12/96 faced with a rising PAP and an inability to reduce his PSA to non-detectable, he added PC-SPES at 6 capsules. His PSA on 12/26/96 was .003. On 4/11/97 he stopped lupron and Eulexin and on 5/13/98 thalidomide was stopped. As of August 2000, with a dose of 12 capsules of PC-SPES and 10 mg of proscar per day, his PSA is .003 using the ultra sensitive test.

He is an active member of several of the Los Angeles area support groups where there are several other survivors much like Harry. He also works with Dr. Strum's Prostate Cancer Research Institute.

When CHT Fails

One of the drugs used by many oncologists when the patient stops responding to CHT is Ketoconazole, brand name Nizoral. It is usually given with aminoglutehimide.

Dr. Stephen Strum is an Oncologist. He answers questions from patients on an Internet site called P2P, (Physician to Patient). You can send e-mail to: p2p@www.prostatepointers.org. Here is part of one of his responses to a patient:

"<My PSA rose again, this time to 14.0 which has totally frightened me. I have a few questions as follows:

1) do you still recommend nizoral when the PSA jumped from 10 to 14 in one week?>

Nizoral or Ketoconazole is an excellent agent for both androgen dependent PC and androgen independent PC. It can be used in combination with other agents due to it being synergistic with drugs such as velban and adriamycin, and perhaps Taxotere.

<2) An oncologist recommends starting chemotherapy with taxotere. Do you agree and do you recommend a particular protocol (a few options seem to have been presented)>

We are using weekly taxotere at 25 mg/M² of body surface area. This amounts to about 50 mg average dose for most men. This is well tolerated. We often combine the taxotere with another agent such as carboplatin or cytoxan and 5 Fluoracil."

Note that the dosage listed above is "25 mg/M² of body surface area." We are all different. The M² means per meter of body surface squared. A man who weighed 150 pounds would not be given the same dose as a man who weighed 300 pounds.

When and if the patient stops responding to one protocol, there are several other drugs. Here are just a few that are often used for chemotherapy:

Adriamycin, Cyclophosphamide, Estramustine, 5-Fluorouracil, Gemcitabine, Mitomycin-c, Navelbine, Nitrogen Mustard, Taxol, Taxotere, Trimetrexate, Vinblastine, Mitoguzone, Doxorubicin, Epirubicin, Mitoxantrone (Novantrone), Strontium 89 (Metastron), Samarium 153 (Quadramet).

Here are a few drugs that are sometimes used in combination:

Cisplatin plus Doxorubicin, Cisplatin plus Etoposide, Methotrexate plus Buserlin, Estramustine plus Doxorubicin, Estramustine plus Etoposide,

Estramustine plus Navelbine, Estramustine plus Taxol, Estramustine plus Vinblastine, Navelbine plus Taxol.

This is not a complete listing of chemo drugs. Many new ones are being investigated and developed.

Dr. Mark Scholz, an oncologist who works with Dr. Stephen Strum had this to say on the Internet to a patient:

The most active chemo agent in prostate cancer is Taxotere. It is much more active than Novantrone. If it is ultimately proven that you have metastatic prostate cancer to the liver then I recommend that you take taxotere 25 mg/m² every week. The side effects are mild and there is at least a 50% chance that it will be beneficial.

Mark Scholz M.D.
Daniel Freeman Hospital
Marina del Rey, California

How The Drugs Are Given

Chemotherapy may be given by different methods. Most often it is given by injection into a vein or intravenously. It may also be injected intramuscularly or under the skin (subcutaneously). It can also be given orally or by mouth, (The prescription may say PO which means Per Os- Os means mouth).

Sometimes the drugs are diluted into a large bag of liquid and given via a 'drip' into a vein in your arm or hand. In these cases, a fine tube will be inserted into the vein and taped securely to your arm.

Another way of giving intravenous chemotherapy is via a fine plastic tube (called a central line) put into a vein in the chest. Unlike the cannula used for the vein in an arm, a central line is inserted after one has been given a general or local anesthetic. Once it is in place, the central line is either stitched or taped firmly to the chest to prevent it from being pulled out of the vein. It can remain in the vein for many months. This will reduce the need for needles when given the intravenous chemotherapy. Blood for testing can also be drawn through this line.

Chemotherapy may also be given by using infusion pumps. The pumps are portable and come in various types. They can be used to give a controlled amount of drugs into the bloodstream over a period of time.

Some of the Side Effects

We are all different and have different diseases. We may not all react the same way to a treatment. But here are some general side effects that one may expect on some of the chemotherapy drugs: Nausea and vomiting,

fatigue, hair thinning and loss, diarrhea and constipation, mouth and gum problems (stomatitis), skin and nail problems, sexual problems, low blood cell counts, gynecomastia, hot flashes, weight loss, weakness, and several other unpleasant side effects.

Many people are able to carry on with their normal life while on chemotherapy. It is important that you do not become depressed or lie in bed and vegetate. Do everything that you possibly can to improve your quality of life. If possible travel, do all the things that you have always wanted to do.

If you have pain, do not hesitate to ask your doctor for pain relief. Don't worry about becoming addicted to pain killers. You may even be able to have an occasional drink of alcohol. Just check with your doctor and make sure that alcohol does not interfere with your medications.

You can find out more about chemotherapy by going to the site below:

<http://www.bethisraelny.org/healthinfo/chemotherapy/index.html>

Clinical Trials

We discuss abstracts later in this chapter. Many of the abstracts are summaries of clinical trials that have been done. There are all kinds of clinical trials. Every drug approved by the FDA has had to go through some sort of trial. Here we are discussing clinical trials for cancers.

Charles J. McDonald, M.D. is National President of the American Cancer Society. In a letter to the U.S. News and World Report, 11/29/99, he says that "... one out of every three women will get cancer in their lifetime and one out of every two men will get it in their lifetime. Currently, only 55 percent of cancer patients are cured. Participating in a clinical trial offers the best and most appropriate treatment for many patients. These are innovative treatments. In the absence of standard treatment, therapy through a clinical trial may be the only way to help a patient. Remember, what was "investigational" a few years ago is often the standard treatment today. Countless Americans are alive today because they participated in a cancer clinical trial".

Should I Join a Clinical Trial?

Here is an article by Israel Barken, MD (619-287-8866)

This article is written for the patient who is about to say, "I'm ready to join a study". Some patients reach this stage because they have exhausted all other avenues of treatment. They are dying, and they have nothing to risk. Therefore, any gain at all is a benefit.

The patient needs to approach joining a study in the most egoistic manner. The most important question is why should I join the study? What is in it for me?

A little background about the nature of clinical studies is helpful here in understanding where the clinical trial you are about to enter has its roots. There are some parts to the process before a trial enters human work. First, the search for new treatments starts in the laboratory where the idea of a drug is tried in test tubes or glass plates. If it is a proposed cancer drug, tumor cells may be grown in culture and the drug is tried there. This is called an "*in vitro*" study. If there is success in this stage, the research goes on to the next phase. If the idea is found to be valid in test tubes, then the treatment is tried on animals. Two factors are tested on the animals: the efficacy of the drug and the safety of the drug. It is absolutely critical for the reader to understand this one point: ***what works in test tubes or on animals may not work at all on humans.*** Therefore, I believe that it is important for the patient to have a disclosure of the initial basic research results and to consult your doctor to help you understand these results.

It is standard practice in Phase I to recruit a small number of patients, usually three patients at each dose level. The dose is raised until either the patient gets sick or the desired result is achieved. Once that level is achieved, six or more patients are then treated with the same level to make sure it is a safe dose. The main question here is: ***How safe is the drug and at what dose?*** The highest dose that can be tolerated is the focus of the experiment here.



In Phase II, the attention is shifted from safety to efficacy. (Note that only about 70% of studies make it from Phase I to Phase II.)

The dose has been determined in Phase I. Now, the highest safe dose is given to 14 patients. If none of these patients respond, the drug is considered worthless. If one patient responds then a total of 30-40 patients are treated. One of the advantages of this phase is that usually there is no randomization of the patients.

Phase III (Note that only about 33% of all trials enter Phase III investigation): In this phase the new treatment is compared to the standard treatment. Phase III is initiated only after the treatment has shown some promise in Phases I and II. Phase III includes a large number of patients in multi-centers. Patients are usually randomized to receive the standard treatment or the new drug.



In a Phase IV study a known proven medication approved by the FDA from previous studies is being checked for a different indication or different dose setting. Data is collected and compared to established treatments.

Patients with very advanced disease and no available treatments may get a drug which is not yet approved and is not available on the market. Under “*compassionate use*”, the drug can be given on an individual basis. For example, thalidomide is available to be given to individual patients who have run out of available treatments through a special arrangement with the FDA.

In summary, only 30% of Phase III studies are submitted to the FDA for approval. Of these, only 20% are eventually approved by the FDA. It may take a company 2-10 years to complete the studies on Phases I, II, and III. It may take the FDA 3-20 years to approve the final product. (No wonder that drugs cost so much).

In looking at an individual clinical trial, here's what you need to know: Each study is carried out according to a strict action plan. This action plan is known as the “*protocol*”. The protocol explains what is done during the period of the study. Each study has to be approved by an “*Institutional Review Board*” or IRB. The IRB is a committee of health professionals, members of the community like clergymen, lawyers and patient advocates. They are responsible for the study being appropriate and avoiding unethical risks.


Selection criteria for studies is a key element in the clinical trial. This is described in the protocol. The eligibility criteria are important for the researchers. They will seek to create groups of similar patients. *You may not qualify under their criteria*. Before traveling to an institution for the purpose of joining a study, have your doctor make the initial connection with the researchers and make sure you qualify. Two main areas for refusing patients to a study are:

Patient must have good organ function. These include liver function, kidney function, adequate number and function of blood components.

Prior treatment which would make evaluation of the study difficult.

You will receive a document called “*Informed Consent*” which basically explains the study and your rights as a patient. You will be asked to sign this document so take the time to ask questions of the researchers, study it and understand it before signing.

What are the possible benefits you can derive from joining a study? There are many. You may receive treatment in a center of excellence and have a very tightly controlled environment in which you can follow your disease through many tests that otherwise would not have been done.

If the treatment in the study  effective you may be one of the first ones to enjoy a good result. This is especially true with the more advanced phased studies. You may have the cost of your care covered by funds provided for the study. By being part of the study you may feel good by doing something altruistic for society.

There are also some possible drawbacks to be aware of when joining a study. They are:

New treatments under study are not always better than standard treatments. You may suffer from side effects that even the researchers did not suspect. You do not have any control over which arm of the study you are assigned to. Neither does your referring physician. You may get a placebo in certain instances.

You may incur some costs for your medical care that will not be covered by your insurance so be alert and check the financial rules of the study very carefully.

What are your rights as a patient contemplating joining a study?

You and only you have the right to choose a study versus standard existing treatments. It is wise to involve your own doctor in this decision.

You have the right to leave the study at any time without any need to give any explanation.

You have a right to have your privacy protected.

You must be given an Informed Consent document to read and sign. All the facts of the study should be given to you. This should include explanations about the treatment, tests, risks and benefits and financial coverage.

Any new information while you are on the study should be given to you. You have the right to ask the doctors how the study is going with other patients and you should get honest answers.

CancerBACUP has an excellent web site with lots of information about clinical trials, sexuality and most other aspects of what you can expect while on chemotherapy. Visit their web site at:

<http://www.cancerbacup.org.uk/info/chemotherapy.htm>

National Cancer Institute (NCI)

The National Cancer Institute is a part of the National Institute of Health, a branch of government. It is an excellent resource and provides lots of information. Many of the items are in blue text. This means that they are automatically linked to a page or another URL (Uniform Resource Locator) site that has more information about that item. Just click on the blue text and it will take you to the new area. There is usually one or two arrows at the top left corner of the page. If you click on the left pointing one, it will take you back to the last page you were on. Click on the right pointing one will take you to the next page.

You can access the NCI by phone, fax, e-mail, or on the web:

Telephone

Cancer Information Service (CIS)

Provides accurate, up-to-date information on cancer to patients and their families, health professionals, and the general public. Information specialists

translate the latest scientific information into understandable language and respond in English, Spanish, or on TTY equipment.

Toll-free: 1-800-4-CANCER (1-800-422-6237) *TTY:* 1-800-332-8615

Clinical Studies Support Center

Provides information for patients and physicians seeking information on the National Cancer Institute clinical studies at the Clinical Center in Bethesda, Maryland. Available Monday-Friday, 9 am-5 pm EST.

Toll-free: 1-888-NCI-1937

E-Mail

CancerMail

Includes NCI information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, send e-mail to

cancermail@icicc.nci.nih.gov with the word "help" in the body of your message.

FAX

CancerFax®

Includes NCI information about cancer treatment, screening, prevention, and supportive care.

To obtain a contents list, dial **301-402-5874** from a fax machine hand set and follow the recorded instructions.

Clinical Trials

NCI's trials database, [PDQ®](#) (see [User's Guide](#) for search tips)

New! [Conducting Trials: Resources for Health Professionals](#)

Educational Resources

[Taking Part in Clinical Trials: What Cancer Patients Need to Know](#)

[Taking Part in Clinical Trials: Cancer Prevention Studies](#)

[Cancer Facts](#) -- brief summaries of subjects related to clinical trials, provided by the Cancer Information Service

[Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial](#) -- this site provides information about participation in the PLCO trial, a large-scale effort to determine whether screening healthy people for these cancers can result in early detection and lower death rates.

For information about clinical trials taking place at the NCI/National Institutes of Health campus in Bethesda, Maryland, see the [Bethesda Campus Clinical Trials](#) site.

Bulletin: [High Priority Trials](#) Seeking Patients

[Certificates of Confidentiality: Background Information and Application Procedures](#)--Certificates of Confidentiality allow researchers to avoid the involuntary release of any portion of research records containing information that could be used to identify study participants.

General Cancer Information

[CancerNet](#) -- CancerNet contains material for health professionals, patients, and the public, including information from PDQ® about cancer treatment, screening, prevention, supportive care, a searchable listing of clinical trials, and CANCERLIT®, a bibliographic database.

For a complete introduction to many types of cancer, see the [What You Need to Know](#) series.

[Cancer Information Service](#)-- a national information and education network
[Cancer Facts](#) -- a collection of fact sheets that address a variety of cancer topics.

[Questions about Cancer](#) -- This page offers Frequently Asked Questions and information about how to ask your own questions electronically or by telephone.

Web Page

The [Main NCI Page](#) at <http://www.nci.nih.gov/> is NCI's primary web site. It contains information about the Institute and its programs. It has a wealth of information.

[Rex](#) is a site that includes news, upcoming events, educational materials, and publications for Patients, Public, and Mass Media.

Some HRPC Abstracts

The Internet is a fantastic way to find out about chemotherapy and treatments. If you visit the American Society of Clinical Oncologists (ASCO) web site at www.asco.org and do a search for Hormone Refractory Prostate Cancer, you will find several abstracts.

You will find several abstracts at the American Urological Association (AUA) web site. You can search their web site at www.auanet.org.

The web sites are updated frequently. They can let you know of new research and discoveries. By all means you should have a computer that will allow you to take advantage of these resources.

Many of the abstracts are about Docetaxel, Estramustine/Etoposide, SU101, Paclitaxel, Estramustine and Carboplatin,

The Protocol of Dr. Bob Leibowitz (310-229-3555)

I strongly recommend applying our most effective systemic treatment "up front." I believe it is a major mistake to "save your best weapon for last." The best time to attack prostate cancer is the first time. If it is time to consider chemotherapy, use it now, and use the most effective treatment; essentially with no exceptions.

Do not wait and allow prostate cancer cells the time to mutate and become more aggressive. We know cancer cells undergo additional, molecular biological hits (mutations) that make them more resistant to treatment. These additional hits or mutations apply not only to hormone sensitive cells, but also hormone resistant. Hormone resistant cells continue to undergo additional molecular biological changes and mutate to ever more resistant cells. Hit them hardest early.

I give Taxotere-based chemotherapy, either E.T./C.D. or T/E/D for about 16 weeks. What follows is the treatment program I usually recommend to my patients. I cannot recommend this to anyone who is not my patient. That decision can only be made by you and your oncologist.

T/E/D protocol:

I began using what I called the T/E/D protocol about one and one-half years ago. This consists of weekly low dose Taxotere, along with Emcyt two days a week and Decadron two days a week. I treat three weeks in a row, then one week off.

At times, I have added a fourth medicine, carboplatinum (once a week, intravenous), and I call the four drug program E.T./C.D. (the initials of each of the four medicines Emcyt, Taxotere, Carboplatinum and Decadron).

All of the men are also on once a month Aredia and daily Proscar. For the E.T./C.D. protocol, I simply add carboplatinum, 100 to 125 mg/m² (total dose 200 mg or 250 mg rounded off) each week. So far, I have not seen any extra toxicity by adding carboplatinum, except for some mild reversible hair loss. I have administered several hundred doses of carboplatinum to date, and this observation is most impressive and accurate. I predict that the E.T./C.D. program will ultimately be shown to be even more effective than T/E/D. I have begun to recommend using prophylactic Coumadin, a blood thinner to prevent blood clots (thrombophlebitis). There is a risk of blood clots from Taxotere/Emcyt or Taxol/Emcyt.

These two Taxotere-based chemotherapy regimens debulk cancer much more effectively, in my opinion, than Nizoral-type, alternate hormone blocking regimens, and this puts you in remission. Then use Nizoral or aminoglutethimide as maintenance therapy, to maintain your remission.

I also urge liberal use of Aredia. I often utilize Aredia plus E.T./C.D. or T/E/D as my first treatment for men with hormone resistant or hormone refractory prostate cancer.

Summary

There are studies that appear to show an improvement in survival in some men treated with chemotherapy. Trials are ongoing to evaluate chemotherapy that is given early in the disease, before the patients becomes hormone refractory.

A number of drugs are showing promise including combinations of drugs. Mitoxandrone and Prednisone have been shown to improve quality of life. The combinations of Taxotere and Estramustine Phosphate have yielded some significant PSA responses.

Gene therapy, antiangiogenesis drugs, drugs that block the cell's signal that inhibit the cell from aging (anti-sense bcl-2) are among some of the more exciting therapies being evaluated.

Lots of research and clinical trials are being done. Eventually they will find a cure for cancer or at least find a way to keep it from killing you.

We hope that you can find a treatment that will work for you-

A Sad Note

In the first edition of this book, in this chapter, we wrote about Scott Barker, Len Snyder and Russ Ingram. They all put up a good fight, but lost the battle. This book is dedicated to them and the other thousands of men who have also lost the battle.