Chemotherapy Considerations When Docetaxel/Taxotere Appears to be Failing

Compiled by Charles (Chuck Maack) – Prostate Cancer Advocate/Activist

Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued research and study in order to serve as an advocate for prostate cancer awareness, and, from a activist patient's viewpoint, to help patients, caregivers, and others interested develop an understanding of prostate cancer, its treatment options, and the treatment of the side effects that often accompany treatment. Readers of this paper must understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as my opinion, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing prostate cancer care.

I am sorry to learn of anyone appearing to have failed the usual first-line chemotherapy medication, docetaxel/Taxotere. There are several medications that administered along with Taxotere bring about a more synergistic effect of that Taxotere. Often, when Taxotere appears to be failing, changing chemo medications to accompany the Taxotere can result in the Taxotere becoming more effective. Here are combinations, for example:

Cabazitaxel/Jevtana

Sipuleucel-T/Provenge

A recent study (2015) found that a small group of men responded to a combination of carboplatin + prednisone + everolimus. You can review this paper and discuss with your physician whether this three-medication protocol is available. See: http://tinyurl.com/ol9bo5b

In 2011, Abiraterone/Zytiga was approved by the FDA for prescribing when docetaxel/Taxotere accompanied by any other chemo agent has failed. Abiraterone/Zytiga is also going to trials for those patients who are failing androgen/hormonal deprivation medications rather than moving to High or Low dose ketoconazole in the hope to avoid moving to chemotherapy agents. Abiraterone/Zytiga has been found to not just block testosterone produced by the testicles, as well as testosterone metabolized from androgen precursors produced by the adrenal glands, but also to block dihydrotestosterone produced within the

prostate cancer cell. This is important since dihydrotestosterone (DHT) is an up to five or more times more powerful stimulant to prostate cancer cell growth than is testosterone.

Irofulven with prednisone can work for several months; see:

http://www.renalandurologynews.com/drug-may-benefit-docetaxel-failures/article/35729/

A May 2008 report describes Sagopilone plus prednisone promising in combination as well as promising to those for whom docetaxel/Taxotere is no longer working. (See: **http://tinyurl.com/5m59xr)**

Ixabepilone has been found to have activity when docetaxel/Taxotere shows failure.

Per Medical Oncologist Stephen Strum, specializing specifically in research and treatment of recurring and advanced prostate cancer since 1983:

TAXOTERE weekly or every three weeks? And combination drugs for synergy.

< Stephen Strum, MD >
I have been one of the first PC medical oncologists to use Taxol and Taxotere. In fact, my practice was instrumental in convincing Medicare to allow payment for Taxanes prior to the FDA's approval. Thus, I have had a huge experience in using both Taxol and Taxotere in men with PC. I have tried the every 3 week regimen, gone to the weekly since the patient tolerance and QOL (Quality of Life) was vastly superior using weekly, gone back again to the every 3 week regimen and finally came to the conclusion that the QOL was so superior using weekly Taxotere or Taxol that I could not bring myself to subject men to the higher dose, every 3 week regimen.

Moreover, in ALL of oncology it is the combination regimens that prove superior than the single agent regimens. Thus, I aim to use combinations that have been shown to be synergistic. These are agents (some supplements, some other drugs) where peer-reviewed publications (PRP) indicate synergy:

GLA, CLA, Octreotide, ATRA, Decitabine, DIM, Silybinin, Celebrex, methylselenocysteine, carboplatin, gemcitabine, calcitriol, exisulind (clinoril), zometa, EGCG, DES,

Pioneers embrace new ideas

Others who fear to know, strain to maintain the status quo

Therefore, for me, I want to use weekly Taxotere with weekly flat dose Carboplatin and ideally add Celebrex at 200 mg bid or perhaps even 400mg bid. Celecoxib = Celebrex.

Altorki NK, Keresztes RS, Port JL, et al:
Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer. J Clin Oncol 21:2645-50, 2003.

PURPOSE: Preclinical studies suggest that treatment with a selective cyclo-oxygenase-2 (COX-2) inhibitor may augment the antitumor effects of chemotherapy. In this study, patients with non-small-cell lung cancer (NSCLC) were preoperatively treated with celecoxib in combination with chemotherapy. End points were toxicity, response rates, and measurement of intratumoral levels of prostaglandin E2 (PGE2).
METHODS: In this phase II trial, 29 patients with stages IB to IIIA NSCLC were treated with two preoperative cycles of paclitaxel and carboplatin, as well as daily celecoxib, followed by surgical resection. Levels of PGE2 in the primary tumors and adjacent normal lung tissue were compared in 17 study patients versus 13 controls, who received preoperative paclitaxel/carboplatin without celecoxib.
RESULTS: All patients completed preoperative chemotherapy, and 26 completed preoperative celecoxib. The overall clinical response rate was 65% (48% with partial response; 17% with complete response). Grade 3 or 4 neutropenia was observed in 18 patients (62%). Twenty-eight patients were explored and underwent complete resection of their tumors. There were no complete pathologic responses, but seven patients (24%) had minimal residual microscopic disease. The addition of celecoxib to a regimen of paclitaxel and carboplatin abrogated the marked increase in levels of PGE2 detected in primary tumors after treatment with paclitaxel and carboplatin alone.
CONCLUSION: In comparison with historically reported response rates, these data suggest that the addition of a selective COX-2 inhibitor may enhance the response to preoperative paclitaxel and carboplatin in patients with NSCLC. Moreover, treatment with celecoxib 400 mg twice daily was sufficient to normalize

the increase in PGE2 levels found in NSCLC patients after treatment with paclitaxel and carboplatin. Confirmatory trials are planned.

PATIENT QUESTION: Can you give me some guidance on how best to explain to our oncologist why I'm requesting Carboplatin to be added to his regimen? I'm anticipating that he may tell me that the treatment he prescribed is the standard based on the NCCN guidelines, so I want to be prepared to respond to this. Also, of the other agents that you listed to add to his regimen, would you know which is the least toxic with the least side effects? Is this something that could be added later on after we observe how his body responds to Taxotere and Carboplatin?

Dr. Strum Reply:

This is a huge problem since the prevailing mentality among physicians is NOT to think outside the box--especially if an HMO is involved. The rationale should be for any serious illness to go for the best possible chance of a CR (complete remission) in the face of metastatic disease. The quantity of life is at stake so why not pull out the stops. I will give you an example that goes back to the 70's--before I became totally immersed in PC.

I evaluated a woman with BC (breast cancer) who had 30+ nodes involved in her axilla (armpit area). In BC, such heavy nodal involvement connotes a terrible prognosis with a shortened life span. I placed the woman on a weekly regimen of Cytoxan, Vincristine, Methotrexate and 5-FU that was based on a very promising paper by Cooper et al. I have spent a lot of my life in medical oncology looking for ways to improve patient QOL. I was one of the early pioneers in the use of new anti-emetics in treating cancer patients receiving highly emetogenic chemotherapy (drugs that make the cancer patient throw up). I was the senior author of one of the earliest papers published in JCO on the use of the Port-A-Cath. In PC, I wrote the landmark paper on AAD (anemia of androgen deprivation) and later the correction of the anemia with EPO (erythropoietin). In any event, I treated this woman for 2 years with this weekly regimen despite protestations from insurance company and lack of agreement by other colleagues in the community. A few years ago, I heard from an oncologist who had seen this patient in follow-up and who was shocked that the patient was disease-free after thirty years. In PC, there is a corollary in the paper by Servadio et al. This used a 3-year regimen of Cytoxan + 5-FU + local RT + DES. See the PCRI (Prostate Cancer Research Institute) article at

http://www.prostate-cancer.org/resource/pdf/Is1-1.pdf>http://www.prostate-cancer.org/resource/pdf/Is1-1.pdf.

I do not, nor have I ever, practiced the "Standard" of care. For me, the standard is always 10-15 years behind. Just look at the articles written in Insights and authored by me and you will have 10 year follow-up regarding this remark.

Regarding what agents to choose for synergy.

Here is a list of agents with peer-reviewed publications (PRP) relating to synergy with Carboplatin:

Synergy with Carbo: Silibinin, Celebrex, Iressa, NDGA, RT & theanine for Carboplatin.

You and your medonc need to simply do a PubMed search.

Clearly, silibinin, celebrex, theanine are simple agents to use. Reading the articles is important since the timing of administration of the agent(s) is important in relation to the chemotherapy.

There are many second lines of chemotherapy involving a reasonable number of drugs. These include agents such as Novantrone, Adriamycin, Velban or Navelbine, Mitomycin C, Dexamethasone, 5-fu, Cytoxan. There are also other agents that may or may not have been used such as HDK (high-dose ketoconazole) or aminoglutethimide (AG) + hydrocortisone, DES, estradurin, or DES-DP. There are newer agents such as Abiraterone, open to men who have progressive PSA increases and who have failed a taxane regimen."

More from Dr. Strum:

"I think the literature on using Abraxane (nab-paclitaxel) after Taxotere failure is compelling to use this drug. Also, it can be combined with high dose Calcitriol or with Estrogens. Other chemo agents that might work well include:
Mitoxantrone
Velban or Vinorelbine either alone or in combination with low dose Mitomycin C. I have used Velban 2.5-5mg weekly with Mitomycin C, 2.5-5mg weekly. This is a good regimen but requires CLOSE watch on the CBC and Platelet count and knowledge of how these agents work."

An outstanding Urological Oncologist who was involved in the research and development of cabazitaxel/Jevtana may be one to email and ask what he would recommend should a prostate cancer patient have failed docetaxel/Taxotere in combination with cabazitaxel/Jevtana. Here is contact info:

Oliver Sartor, Professor of Medicine and Urology, Tulane Medical School, 1430 Tulane Ave., New Orleans, LA 70112, 504-988-2750, fax 504-988-5059, email osartor@tulane.edu

A return to High Dose Ketoconazole accompanied by Hydrocortisone along with an LHRH agonist and 5AR inhibitor (dutasteride/Avodart preferred) has been found to kick in at times when docetaxel/Taxotere and combinations are showing failure. There are several chemotherapy agents that can be employed when others appear to be failing. We would hope one's Medical Oncologist takes the time to determine what those other agents might be.

Several other medications are being researched or are in trial. It behooves everyone who has been diagnosed with recurring or advanced prostate cancer to involve themselves in research and study of the many medications involved in reining in prostate cancer. Encourage your Medical Oncologist to do the same. When you locate important information, email it to your physician or print it and take it to him/her and persist in discussion as to the pro's or con's of what you have found.

Medical Oncologists who are considered at a special level of expertise specifically in research and treatment of recurring and advanced prostate cancer usually require travel for an appointment and evaluation as to what has been done and what could/should be done next. Often, once a protocol is determined, these Medical Oncologists will call/contact the patient's oncologist to perform periodic diagnostics to make sure the protocol is working. Sometimes local Medical Oncologists are willing to collaborate with these experts, other times their ego gets the best of them and they refuse to listen to someone with likely much more expertise when it comes to the treatment of recurring or advanced prostate cancer.

To the East is Medical Oncologist Charles E. "Snuffy" Myers. His contact info is:

Charles E. "Snuffy" Myers (Does not accept insurance. Fee for consultation services), American Institute of Disease of the Prostate & Foundation for Research and Education, P.O. Box 307, Free Union, VA 22940, 960 Bent Oaks Drive

(Office), Earlysville, VA 22936, Tel: 434-964-0212 Email drmyers@prostateforum.com. Website: www.prostateforum.com. Earlysville is unincorporated and not shown on most maps. When flying in for an appointment, Charlottesville, Virginia has the closest airport and from the airport, just a few miles from Earlysville. Charlottesville is home of Monticello and the University of Virginia. Wikipedia says Earlysville is 18 miles north of Charlottesville, so the airport is apparently somewhere in between.

To the West, meaning far West:

Mark Scholz and Richard Lam, 4676 Admiralty Way, Suite 101, Marina del Rey, California http://www.prostateoncology.com (310) 827-7707 richard@prostateoncology.com
(Mark Scholz and Richard Lam are partners in Prostate Oncology Specialists, Inc.)

Bob Leibowitz, Los Angeles, California, Compassionate Onc Medical Group, 2080 Century Park E, Suite 1005, Los Angeles, CA 90067-2009, Tel: 310-229-3555, email: info@compassionateoncology.org, Website: www.compassionateoncology.org (Requires initial $550.00 fee, then your insurance coverage for treatment)

To the Northwest:

OREGON

Stephen B. Strum, Ashland, Oregon, Contact Miwha Strum at miwha@sbstgrum.com or call her at 541-201-0219 to arrange consultation (Does not accept insurance. Fee for consultation services). The expertise of this renown Medical Oncologist is well known as the result of the guidance he has provided on the Us TOO p2p prostate cancer support list. I do believe that at the end of 2011 he may be retiring from consultation practice.

Ralph Weinstein, Rose Quarter Cancer Center, 265 N. Broadway, Portland, Oregon (Associated with Northwest Cancer Specialists) Tel: 503-280-1223 http://www.nwcancer.com/rose_quarter_map.php

Tomasz Beer. Oregon Health & Science University Cancer Care Center, Center for Health & Healing, Portland, Oregon, 503-494-6594 (Principal researcher of transdermal estradiol/TDE)

SEATTLE

Celestia S.Higano, Associate Professor, Department of Medicine, Division of Oncology, Seattle Cancer Alliance/University of Washington (206) 288-7222.

To the North:

MICHIGAN
Maha Hussain or Ken Pienta, U-M Comprehensive Cancer Center, 1500 E. Medical Center Drive, CCGC 6-303, Ann Arbor, MI 48109-0944, Tel: 734-647-8903

To the Northeast:

NEW YORK
Daniel Petrylak, M.D. Associate Professor of Medicine Office Location Columbia University Medical Center Irving Pavilion Floor 9 Room 919 161 Fort Washington Avenue New York, NY 10032 Phone (212) 305-1731 Fax (212) 305-6762

Howard Scher, Memorial Sloan Kettering Cancer Center, New York City http://www.mskcc.org/mskcc/html/17754.cfm then click on name.

NEW JERSEY
Robert S. DiPaola, M.D., New Jersey University of Medicine, Robert Wood Johnson Medical School, 195 Little Albacy St., Suite 2038, New Brunswick, NJ 08903, telephone 732-235-2465, fax 732-235-7355 dipaolrs@umdnj.edu stats: http://rwjms.umdnj.edu/news_publications/news_release/2008_releases/090908_CINJ_DiPaola.html or try **http://tinyurl.com/nfkwmb.**

In the MidWest:
KANSAS
Bassam Mattar, Cancer Center of Kansas (CCK), Associate Clinical Professor, Program Director of Bone Marrow Transplant, University of Kansas School of Medicine - Wichita, Wichita, Kansas, Heritage Plaza Medical Building 818 N. Emporia, #403, Wichita, KS 67214, (316) 262-4467
http://doctor.medscape.com/bassammattarmd
http://www.cancercenterofkansas.com/Doctors/BassamMa.htm

To the South and Southwest:

TEXAS

Christopher Logothetis, University of Texas M. D. Anderson Cancer Center, Dept. of GU Medical Oncology, 1515 Holcombe Blvd., Houston, Texas Tel: 713-745-7020 for new patients or 713-792-2830

Robert Amato, 6560 Fannin St # 2050, Houston, TX 77030-2783, Tel: (713) 441-7930, email robert.amato@uth.tmc.edu

Thomas Hutson, D.O., Pharm. D, Texas Oncology-Baylor Charles A. Sammons Cancer Center, 3410 Worth Street, Dallas, TX 75246, Telephone: 214-370-1000, webpage: http://www.texasoncology.com/doctors/Thomas_Hutson/

ARIZONA

Frederick Ahmann, M.D., Arizona Cancer Center, University of Arizona, 1515 N. Campbell Ave., Tucson, AZ 85724, telephone (520) 626-8096, email: rahmann@azcc.arizona.edu, website: http://azcc.arizona.edu/profile/frederick-ahmann

In other countries:

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Steven Tucker, M.D., website: www.drsteventucker.com, email: drsteventucker@gmail.com (or) prostatehelp@gmail.com telephone USA: 310-594-3301, Singapore: +65 8228 2653

ISRAEL:

Avishai Sella, avisella@netvision.net.il (highly recommended by Arie Belldegrun, MD, FACS, Professor & Chief of Urologic Oncology, Roy and Carol Donmani Chair in Urologic Oncology, David Geffen School of Medicine at UCLA)

CANADA/Toronto:

The following two urologists are listed here because of their involvement beyond urology in research and study of the treatment of prostate cancer at all levels of progression:

John Trachtenberg, Prof. Director Prostate Center, Princess Margaret Hospital, 610 University Ave. Toronto ONM5G2M9, Canada, telephone: 416-946-2100, Fax: 416-598-9997, Mobile: 416-473-3758 email: john.trachtenberg@utoronto.ca

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GREAT BRITAIN:
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Dr. Rob Thomas, Consultant Clinical Oncologist and Director, The Macmillan Primrose Unit, Bedford Hospital South Wing, Kempston Road, Bedford MK42 2RJ, telephone 01234 355122.
(The Primrose Unit is a small NHS and private facility. It is a satellite clinic to the Oncology Department at Addenbrooke's Hospital in Cambridge, which is where radiotherapy treatment takes place and shares specialist staff with Addenbrooke's)

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I am sure there may be others, but the forgoing are those for whom I am either personally aware or have been provided promising reports by prostate cancer patients.