Bill Aishman: Can Chemotherapy Extend Survival for Hormone Refactory Prostate Cancer Patients?

http://www.cancer.prostate-help.org/cachsuv.htm

A patient’s suggestion that judicious selection and sequencing of chemotherapy protocols can extend a quality life for HRPC patients.

"It is sobering to note that the median survival of HRPC is less than one year, and no agent...has yet been shown to improve the median survival of such patients." (40) Isn’t it somewhat perversely satisfying to know that the Long White Coats (LWC) can be really wrong as they omnipotently forecast our deaths?

SUMMARY

Thousands of prostate cancer chemotherapy trials and reports document a cohort of described patients, the protocol of treatment with a chemotherapy agent or combinations of specific agents, the response rate thereto, median duration of response, median duration of survival, and occurrences of adverse side effects. All of the trial abstracts/reports conclude that while the treatment was effective, no survival benefit resulted therefrom. Therefore, can we assume (and it is sometimes stated) that these very expensive and debilitating treatments are only palliative?

HRPC chemo protocols report median durations of survival of up to twenty-two months, but most are much shorter. Therefore, are we to assume that the average man in the treatment dies within a few months after beginning the treatment? All of us know that when a chemotherapy protocol is exhausted, or produced inadequate response, another chemotherapy protocol is initiated. Yet, I can find no reports or documentation of any semblance of suggested sequencing of protocols. Rather, we are only subjected to a specific suggestion of our medical oncologists for the next treatment and he never presents/explains a matrix of available salvage protocols for the patient to consider. (The best summary of the array of chemo treatments I have seen is in LEF, pp. 607-615 = well worth studying.)

I suggest that it is incumbent on the patient to familiarize himself with all available protocols and chemotherapy agents, even for his first entry into the chemotherapy world of treatments. Most oncologists have drug company relationships or personal experiences with particular chemotherapy agents and either are not familiar with the matrix of offerings, or have no interest in informing the patient of alternative agents/treatments. Also, most oncologists do not discuss protocol response rates, median duration of response, median duration of survival, or specific data regarding all of the side-effects resulting from the agents/protocols. Again, I suggest that it is incumbent on the patient to become as familiar as possible with the array of treatments available and become an active participant with his medical team in his treatment program ---and I suggest that a careful orchestration of sequential chemotherapy treatments can prolong quality survival.

Below, I have attempted to present the major protocols and categorize them by response rates, median duration of response, and median duration of survival. By proper sequencing the treatments, we could expect to experience quality extended survival by virtue of responding to each/some of the sequenced treatments?
NOTE

This is a summary update of
Bill Aishman: Chemotherapy For Hormone Refractory Prostate Cancer (HRPC) and
Bill Aishman: Chemotherapy for HRPC - Part 2

To search my references: 1) for abstracts in journals, go to Pubmed 2) for the ASCO abstracts, go to ASCO Abstracts. Numbers between parentheses refer to the references at the end.

ACRONYMS

bid -- twice/day
tid -- three times/day
Q21 -- every 21 days
po -- orally, by mouth
PCa -- prostate cancer
TX -- treatment
RR -- response rate = % of patients that experienced >50% reduction in PSA
MDR -- median duration of response = months after TX start to disease progression.
MDS -- median duration of survival = months after TX start to death, OR LAST PATIENT CONTACT.
mg/m2 -- milligrams of agent per meter squared of skin surface; easily calculated by your doctor based on height and weight.
DVT -- deep vein thrombosis = blood clots.
TX --- treatment.

DISCUSSION

I propose the following matrix as selection and sequencing of chemo protocols for HRPC as they relate to effectiveness, side-effects, and patient tolerance. I suggest that all HRPC patients who are considering chemotherapy study the matrix, research the abstracts/reports, and have open discussions with your oncologist regarding each alternative protocol and its application in your particular case. If he/she does not have the time or interest to discuss these with you, change medical teams.

Assuming that the patient has exhausted CHT (Casodex/Lupron, or equivalents), AAWR (Casodex withdrawal), H/LDK + HC, PC SPES, or other estrogen treatments-- there are two non-chemo (steroid) TXs that should be considered before chemo, or prolonging time ‘off’ chemo should you respond to a chemo protocol (PSA <4.0) and elect intermittent chemo TX (I did not respond to either of these, but I was heavily-TXd before trying them):

a) Low-dose dexamethasone (Decadron) @ 0.5-2.0 mg/day reported a RR of 50 to 79%, MDR of 2-15 months, and substantial radiographic evidence of disease regression. (1, 2, 3).

b) Low-dose Prednisone @ 7-10 mg/day reported significant palliation, 12-24% PSA ‘suppression’, and MDR of up to 4+ months. (4,5,6,7)
The sequential chemo protocols I suggest that are effective to prolong quality survival are:

1) Weekly single agent Taxotere (docetaxel)---Taxotere is one of the taxanes (Taxol is the other)---the taxanes ‘freeze’ the cancer microtubule spindles and thus inhibit microtubule depolymerization, attenuate bcl-2 and bcl-xl expression, and produce apoptosis (death). "Interest has shifted to administration of docetaxel on a weekly basis, which is associated with a more favorable safety profile than the conventional every 3-week schedule" (8). This protocol has lower responses than those that include Emcyt, but the safety/side-effect profile is preferable. Recent studies report RR of 41% (27% had a decrease of >80%), MDR 5.1 months (0.9-18.2) and MDS of 9.4 months (1.6-18.2) (9); earlier reports reflect RR of 47% and well-tolerated. Scholz MC et al reported RR of 61%, MDR of 5.6 months. (10) As my earlier referenced papers reflect, I responded for 17 months to this protocol with a PSA nadir of 1.2.

2) If your schedule denies being in a chemo room 3 out of 4 weeks per month, Q21 single agent Taxotere is a viable next alternative with acceptable toxicity profiles. Picus J reported RR of 46% (20% had >80% PSA reduction), MDR of 9 months (2-24), and MDS of 27 months with Taxotere @ 75 mg/m2. (11). Hussain A et al reported RR of 57% with minimum toxicities; Q21 Taxotere @ 70 mg/m2. (12) As explained in my earlier papers, I elected weekly Taxotere for the favorable toxicity profiles and the antiangiogenic properties of the weekly protocol vs. the ‘kill ‘em all’ approach of the Q21 protocols, but responses and durations of response are similar for weekly or Q21 single agent Taxotere.

3) If the single agent Taxotere protocols exhaust or responses are not acceptable, Emcyt (estramustine) can be added to the single agent Taxotere. Emcyt is nitrogen mustard linked to estradiol with antimitotic (anti-growth) properties; it binds to tubulin and microtubule proteins and disrupts the nuclear matrix (it might also inhibit p-glycoprotein, a multidrug resistance protein); it has a half-life of 50-100 hours; as a single agent, Emcyt has a 37% RR (13), but has "..more than additive antitumor activity.." when combined with other microtubule inhibitors (taxanes). (14) But, Emcyt has a DVT potential of up to 25%, even with coumadin and INRs >2.0, and continues to be problematical as this condition is serious and TX-limiting.

However, results are improved by adding Emcyt to Taxotere. "It can be concluded that prostatic tumors are highly sensitive to chemotherapy and that a new threshold of antitumor activity has been inaugurated based on the significant activity of docetaxel/estramustine in patients with HRPC. Docetaxel is one of the most active agents in this patient population..." (8) Copur MS et al found weekly Taxotere + Emcyt RR of 76% (56% had >75% decrease), MDR of 13 months, and MDS of 18 months. (15) Kosty MP et al reported RR 71.4% (35% > 75% reduction in PSA). (16)

An interesting report is Rajasenan KK et al, a study where HRPC patients exhausted Q21 Taxotere + Emcyt (disease progression) and switched to weekly Taxotere + Emcyt with a renewed RR of 70% and concludes that weekly Taxotere + Emcyt has significant activity in HRPC patients who progress following Q21 (17)---this switch-over result is interesting re sequential TXs.

4) The Q21 Taxotere + Emcyt protocols are the most effective of all the chemo treatments for HRPC. While there are numerous trials/reports regarding Q21 Taxotere + Emcyt, the milestone reports are: (A.) Petrylak et al with a RR of 75% (45% had >80% PSA reduction) and MDS had not been reached; moreover, he introduces intermittent TXing if the PSA reaches a nadir of <4.0; this report shows intermittent ‘off’ time of 14-28 weeks before successfully re-TXing with the protocol (18);
he subsequently reported on the same cohort as a RR of 82% and MDS of 22.8 months (but he questions the efficacy of adding Emcyt vs. the side-effects). (19); and (B.) Saverese DM et al later reported RR of 68% (57% had >75% PSA reduction), MDR 8-10 months, MDS of 20 months, and DVTs of 9%. Of the multitude of chemo trials/TXs for HRPC, this protocol documents superior response, efficacy, and toxicity profiles (with adverse Emcyt reactions a continuing problem).

5) If either weekly or Q21 Taxotere (+/- Emcyt) is exhausted, or there is no response, Taxol is a viable next alternative. As discussed in my earlier paper, p. 6, while both taxanes prevent the mitotic spindle from being broken down by stabilizing the microtubule bundles, Taxotere has a 2-fold higher affinity for microtubules and is TXd at 1/2 the dose of Taxol; and, Taxotere has the advantage of reduced peripheral neuropathies, arthalgia (joint pain)/myalgia (muscular pain) syndrome. (20) Moreover, both taxanes have significant antiangiogenic (prevent blood vessel formation) activity (21) and they are not cross-resistant. (22)

Weekly single agent Taxol was found to have a 75% RR, MDR of 5.3 months (3-8), and one year survival was 83%. (23) Madrueno FD et al found this protocol resulted in 96% response on metastatic sites in BCa. (24) Trivedi C et al reported weekly Taxol with a RR of 39%, with considerable toxicity. (25)

6) If no/inadequate response to single agent weekly Taxol, Emcyt can be added. Weekly Taxol + Emcyt was reported by Singh H et al to have a RR of 75%, MDR of 19.6 weeks, and several toxicities (small number of patients and strange reporting). (26) Taneja S et al, in a dose escalating study, reported @ 60 mg/m2 a RR of 70%, but in a small cohort of patients. (27) Another PH II trial had a 60% RR with this protocol. (28) Again, another study found that 50% of patients had an 80% decline in PSA (strange, small study). (29)

**SUMMARY OF THE TAXANES**

--Taxol/Taxotere protocols report the most effective, patient friendly treatments for HRPC. Considering the RR, MDR, MDS, and toxicity profiles, I suggest the first protocol should be weekly (3/4) single agent Taxotere @ 25-35 mg/m2; followed by adding low-dose Emcyt; next try Q21 Taxotere w/ or w/o Emcyt; then switch to weekly Taxol @ 50-70 mg/m2-- and, add Emcyt if no/inadequate response. If these are exhausted or inadequate response results:

7) Weekly Adriamycin (doxorubician) @ 20 mg/m2---Adriamycin is an old drug used in many cancer types; it differs considerably from the taxanes in that, as an anthracycline, it affects the cells by effecting single- and double strand DNA breaks; its activity is also very cardiotoxic and exhibits this aspect as signs and symptoms of congestive heart failure; thus it has a life-time maximum dose allowed of 550 mg/m2. (30) I can find no trials for weekly single agent Adriamycin; my only reference is to a p2p post from Scholtz M on 10 August 2000 wherein he recommended (he ‘favors’) weekly (3/4) low-dose Adriamycin @ 20 mg/m2 for patients who have progressed on Taxotere. Given Scholz’s reputation and his reported results with weekly Taxotere (10), I would rely on his advice.

8) Add Emcyt to weekly Adriamycin---Culine S reported a 58% RR, MDR of 3 months, and a significant regression of pain and soft-tissue disease. (31)

9) Add Cytoxan to weekly Adriamycin ---Cytoxan is considered pharmacokinetic with Adriamycin; Small, in a Q21 study of Adriamycin + Cytoxan (+ C-GSF), reported RR of 46% (26% had >75% PSA reduction); MDS of 11-23 months. (32) Cytoxan as a single oral agent @ 50 mg/day is considered metronomic dosing (cytotoxic and antiangiogenic) with a RR of 68% and MDR of 7 months. (33) Also, this Cytoxan protocol might be considered as a stand-alone salvage TX, or as maintenance if response to other protocols allow intermittent chemo treatments.
In a fascinating (but complicated) trial, Logothetis et al administered 2/3 cycles of the Logothetis protocol (34) as introductory chemo—followed by a randomized continuation of: a) single agent weekly Adriamycin (6 wks) w/RR 72%, MDR 7 months (2.3-20.9), MDS 16.8 months (4.4-34.2) + HDK maintenance until progression; vs. b) one SR 89 in-

**SUMMARY OF ADRIAMYCIN**

--after exhausting Taxotere/Taxol, I suggest: a) weekly Adriamycin is a viable TX, b) then add oral CY @ 50 mg/day, c) then add Emcyt, d) or, Q21 Adriamycin + Cytoxan, d) the Logothetis finding is fascinating and well worth exploring; maybe add SM 153 (more effective than SR 89) to weekly Adriamycin?

10) Novantrone (mitoxantrone) is a very old drug that continues to be re-cycled. Currently, oncologists across the US are recruiting for a large SWOG randomized trial of Q21 Novantrone + Prednisone vs. Q21 Taxotere + Emcyt. (36) Therefore, oncologists are again suggesting Novantrone + Prednisone as first-line, or salvage TX. But, rumors are that the objective in the trial are to ‘prove’ that Q21 Taxotere + Emcyt prolong life vs. Novantrone + Prednisone. Well, duh!---numerous trials already reflect that Taxotere + Emcyt RR (80%) and MDS (22 months) are far superior to Novantrone + Prednisone RR (33%) and MDS (10 months). Why enter the randomized trial and risk getting the less effective TX?

Multiple trials of Novantrone report RR of 34%, MDR 175 days (37); RR 4%, but 63% had ‘decreasing PSA’; RR 55% in newly DXd patients (38); RR 48%, MDR 10.5 months in a Novantrone + Prednisone arm vs. RR 24%, MDR 3.8 months in Prednisone only arm (39); one report said that Novantrone caused ‘...significant reduction in pain and suffering in approximately 30-40% of patients with HRPC.’ (40); the benchmark report for Novantrone is Tannock IF which reported a RR of 33% (5% cardiac toxicity) and concludes the TX ‘...provides palliation for some patients with symptomatic...’ HRPC (41); in a complicated study of 133 patients, RR 28% and palliative response of 38% (42); several additional studies added various other chemo agents to the protocol and none had better results than the basic TX.

**SUMMARY OF NOVANTRONE + PREDNISONE**

---while this TX is currently being pushed by oncologists, it only has a RR of about 33% and MDR of 5-10 months, and it is an anthracycline (as is Adriamycin); as such, it has serious side-effects of ‘...left ventricular dysfunction and myelosuppression.’ (destroys bone marrow). (43) Also, since Prednisone alone offers a RR of up to 24% (4,5,6,7), Novantrone only adds thereto for an added 9% RR and no additional MDR?

After exhausting Taxotere, this is my current TX (February, 2002)---after two TXs, my PSA is stable at 29, but my WBC falls to 2.0 (low acceptable 4.2) and GRAN falls to 0.9 (no TX if below 2.0) after each TX, but returns to low acceptable by the next TX = Novantrone hammers your bone marrow, and often requires growth factors (Leukine/neupogen), which have their own set of side-effect to deal with.

11) 5-FU (fluorouracil) --blocks a protein that cancer cells need to copy and repair DNA; it is a really old drug having been administered for 50 years in TXing bowel, head/neck, breast cancer; it is bolus administered (single, large quantity in a short period = squirted) via a cannula; but, within minutes it is catabolized (inactivated); the plasma half-life of 5-FU is 6-20 minutes; historically, response rates rarely exceed 20%; concurrent admini-
stration of leucovorin/eniluracil is required to enhance the binding of 5-FU enzymes in the cancer cell, the combination greatly increases the ACU (concentration x time curve) of the effective availability of 5-FU in the body. Because of these bioavailability problems, produgs (an inert drug that becomes active only after it is transformed or metabolized by the body = converted by liver and tumor enzymes) have been developed and allow daily oral administration, thus ease of administration and assuring continued drug exposure to the cancer cells. (44) The two common 5-FU produgs are:

Uftoral = UFT (tegafur-uracile)--Bristol Myers--- significantly increases the tumor-to-serum and tumor-to-normal tissue 5-FU ratios (minimal affect on normal cells); but, co-administration of leucovorin is needed for additional biochemical modulation (this combination of oral UTF/leucovorin is Orzel). (44)

Several trials (colorectal cancer) of UTF report minimal responses of 9-25% and MDR of 3.5 months. (44) BCa trials report a partial response of 55%, MDR 14 months with 5-FU/eniluracil (45); RR 18%, MDR 23.6 weeks for 5-FU/eniluracil in BCa (46); RR 17%, stable PCa disease in 44% (47)

Xeloda (capecitabine) --Hoffman LaRoche---an oral 5-FU prodrug that is selectively tumor and system activated/converted in the cell to its toxic moiety by naturally produced enzymes (thymidine phosphorylase = TP)----it is completely unchanged in the GI tract and is cell cycle phase specific--TP is higher in tumors than surrounding normal tissues and the sequence of activating the liver and tumor enzymes provides tumor selectivity and decreases toxicity to normal tissues (48)--the prodrug yields substantially higher concentrations of 5-FU in tumors than in plasma or normal tissues and 5-FU levels are much higher than those achieved by intraperitoneal (stomach lining) administration of 5-FU at toxic levels.

Xeloda is more effective at a wider dose range and has a broader spectrum of antitumor activity than 5-FU or UTF--- it has additional characteristics not found in 5-FU such as potent antimesstatic and anticachectic (weight loss and wasting). (49) Xeloda has high therapeutic potential in TXing cancer; the antitumor activity of Xeloda is greater than those of 5-FU and UTF and much safer, less toxic to the intestinal tract = higher therapeutic indices. (50)

I cannot find any abstracts/reports re the use of Xeloda in PCa, but I know some men who are using it after exhaustion of other TXs. There are 32 Xeloda abstracts in ASCO 2001, most of them re colorectal and pancreatic cancer and most combine the prodrug with other agents. A 66% response was observed with Xeloda + Cisplatin in AGC (advanced gastric cancer) (51); response of 21%, MDR 221 days in taxane-refactory BCa (52); 53.85% response, MDR 128 days in heavily pre-TXd BCa (53); 28.3% response, MDR 161 days for advanced metastatic BCa (54); 66% tumor control and low toxicity in MBCa after failure of Adrimycin and the taxanes (55); 56% response with Xeloda + Vinorelbine in MBCa (56); 50% response with weekly Taxotere in MBCa that had failed Adriamycin (57).

The reason I got bogged down in 5-FU and the prodrugs is that p2p has, on several occasions, suggested 5-FU as a salvage after exhaustion of Taxotere, and many women with metastasized BCa are taking Xeloda after failure of other chemo protocols.

SUMMARY OF 5-FU/PRODRUGS
---the statistics look promising for BCa and I believe these are worth considering as salvage for exhausted PCa protocols—I hope ASCO 2002 sheds some light on Xeloda for PCa.

12) SERVADIO re-visited---I presented this question in my first chemo paper and still do not understand why there are no reports or practice of this protocol in the US. The proto-
col is: orchiectomy + DES + Cytoxan (cyclophosphamide) + 5-FU.

The Servadio protocol has been used since 1980 in Israel with a cumulative survival rate of 55.5%. This protocol is often mentioned but seldom utilized. Why? Servadio, Nissenkorn, Mukamel first reported the concept in 1980 (58) combining orchiectomy + DES (3 mg/day) + Cytoxan + 5-FU (10 mg/kg X 2 years; then 5 mg/kg X 2 years); 50% tumor shrinkage in 84% of patients; cumulative survival rate during 3.5 years was 76.5%. Servadio et al. again reported (59) 24 Stage D patients and the same hormon/chemotherapy protocol a 79.1% tumor shrinkage, stabilization/partial disappearance of osteoblastic lesions; cumulative survival rates at 5 and 6 years were 63.5 % and 50.78 %, respectively. Servadio again reported in (60) of 36 D2 patients on the same protocol; 75% had bone pain relief; 80% had urinary symptom relief; 82.2% regression or stabilization of the primary tumor; 55.5% stabilization/disappearance of osteoclastic lesions; cumulative survival rate at 11 years is 55.5%. Again in 1992, Servadio et al. reported (61) a retrospective 15 year review of his protocol of hormonotherapy: 50 D2 patients treated on diagnosis; 28% died of the disease; 28% died of other causes; 40% are still alive (14% with clinical disease); he suggests continuation of the protocol utilizing the newer chemotherapeutic agents.

The Servadio protocol is well documented and represents the longest survival statistics. Servadio continually reports that this early aggressive combined systemic therapy intervention in D2 patients is well tolerated with only minimal temporary side effects. One wonders why it has not been investigated and utilized in the US? Servadio began his protocol on diagnosis of D2 with an orchiectomy, but with the advent of Lupron/Zoladex, this would no longer be a necessity and the chemotherapy agents combined in the protocol are well-known and in multiple use in other pharmacokinetic combinations. Why not administer Casodex/Lupron + DES @ 3 mg/day (or less + breast RT) + Cytoxan @ 50-100 mg/day po + Xeloda?—this would be an easy all oral TX with minimal side-effects?

13) MISCELLANEOUS POSSIBILITIES

a) NAVELBINE (Vinorelbine) ---Navelbine is a semi-synthetic vinca alkaloid that interferes with microtubule assembly by inhibiting mitosis (growth) through its interaction with tubulin. There are mixed results of trials; I reviewed 5 trials that had <25% response for Navelbine or N + Emcyt; while Navelbine as a single agent seems less than adequate (MSKCC reports that for all single agent chemo agents, median survival is only 7 months (62))-- Navelbine + Emcyt shows promise: RR 50%, MDR 7 months (5-8) (63); Q21 RR 53% + ‘most pts. in 3rd cycle (64); weekly Navelbine RR 65% (65); weekly: RR 71%, MDR 16 weeks, but ‘toxicity of oral EMP (Emcyt) is still problematic’ (66).

b) VP-16 (etoposide)---VP-16 is known as a topoisomerese enzyme inhibitor; works by blocking the action of the enzyme; the job of this enzyme is to untangle strands of DNA during cell division--failure to do so results in cell death; the enzyme does this by temporarily causing breaks in the strand to allow another strand to pass through; VP-16 prevents the enzyme from completing this repair job and damages DNA. But, it has a rather serious complication in that in 5% of patients, it causes chromosomal defects leading to leukemia, usually fatal. Pienta SK has done most of the work re VP-16.

VP-16 has minimal activity as a single agent (67); VP-16 + Emcyt (both oral) had RR of 50% (>75% PSA reduction in 28%), RR 58% in pts. with bone disease (68); RR 39%, MDS 56 weeks (69); RR 45% in soft tissue and 58% in bone disease, MDS 13 months for both arms (70); RR 45%, MDS 32 months (71); Q21 RR 50%, MDS 208 days (71-693). Therefore, VP-16 + Emcyt seems to be a viable first-line or salvage TX with RR of 50% with MDS of about 1 year.
c) Velban (vinblastine)---an old drug that inhibits microtubule assembly--Velban + Emcyt RR 40% PSA decrease of 25%, MDR 9 months, MDS 11.7 months (73); randomized study: Velban single agent MDR 2.1 months, MDS 9.2 months--Velban + Emcyt MDR 3.7 months, MDS 11.9 months but with significant toxicities in the Velban + Emcyt arm (74); an interesting study by Trudeau Mg et al. found in newly DXd metastatic PCa patients (15), Zoladex + Velban @ 4 mg/m2 weekly (6/8) + Emcyt @ 10 mg/kg po daily X 6 weeks---RR 100% with 11/15 complete responses; toxicity was minimal. (75) Too good to be true? These patients were TXN1M0 or M1--(TX = primary tumor cannot be assessed; N1 = mets in single LN 2 cm or less; M0 = no distant mets; M1 = distant mets); no bone mets.

Bill Aishman

NOTE: I am not a doctor and can not give medical advice. I am not a medical researcher. I am a prostate cancer patient with advanced disease and I performed this layman’s analysis for my own decision-making purposes. In conjunction with a medical team, every cancer patient must make their own decisions regarding treatment options. I make no claim that this analysis is definitive or complete.

I invite any and all additive contributions that will provide patients a framework which will enhance their ability to make informed decisions regarding the use of chemotherapy protocols in their struggle with prostate cancer. There are many innovative chemotherapy agent combinations and protocols currently being investigated. How can we remain updated regarding the latest innovations?

Bill Aishman

February 2002

References:

(1.) Nishimura et al.; Low doses of oral dexamethasone for hormone-refractory prostate carcinoma; Cancer 2000 Dec 15;89(12):2570-76
(3) Storlie et al.; Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma; Cancer 1995 Jul
(4) Tannock IF et al.; Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points; J Clin Oncol 1996 Jun;14(6):1756-64
(7) ASCO 2000 # 1321.
(10) Schulz MC et al; Low-dose single-agent docetaxel (taxotere) id effective and well-tolerated in elderly men with PCa; ASCO 2001 # 2441.
(12) Hussain A et al.; Docetaxel followed by HB in men who fail biochemically after definitive local treatments for PCa; ASC) 2001 # 2392.
(17) Rajasenan KK et al.; Weekly docetaxel alone or with estramustine has significant activity in patients with HRPC previously treated with conventionally dosed docetaxel; ASCO 2001 # 2434.
(18) Petrylak DP et al.; Response and preliminary survival results of a PH II study of docetaxel + estramustine in patients with AIPCA; ASCO 2000 # 1312.
(19) Petrylak DP; Docetaxel (Taxotere0 in HRPC; Semin Oncol 2000 Apr;27(2 Suppl 3):24-9.
(20) http://biotech.icmb.utexas.edu/botany/tax.html
(22) Lockich J; PH I Clinical trial of weekly combined Paclitaxel plus Docetaxel in patients with solid tumors; Cancer 89:2309-14, 2000.
(26) Singh H et al.; Weekly paclitaxel and high-dose estramustine in HRPC; ASCO 2000 # 1494.
(27) Taneja S et al.; PH I trial of Taxol/Estramustine in patients with HRPC; ASCO 1999 # 1364.
(28) Leitner SP et al.; PH II trial of weekly one hour pacliraxel + oral estramustine...; ASCO 1999 # 1331.
(33) Glode LM et al.; Metronomic therapy with low-dose cyclophosphamide and dexamethasone for PCa; ASCO 2001 # 2395.
(34) Logothetis CJ et al.; PH II trial of alternating weekly chemotherapy for patients with AIPCa; Clin Cancer Res 3, Dec 1997:2371-76.
(36) Petrylak D et al.; docetaxel (Taxotere) and estramustine versus mitoxantrone and prednisone for HRPC; scientific basis and design of Southwest Oncology Group Study 9916; Semin Oncol 1999 Oct;26(5 Suppl 17):55-60.
(38) Wang J et al.; Adjuvant chemotherapy in advanced PCa; ASCO 2000 # 1322.
(39) Berry M et al.; PH III study of mitoxantrone/low-dose prednisone vs. low-dose prednisone in pts. w/asymptomatic HRPC; ASCO 2000 # 1321.
(40) Editorial; one hundred thirteen men w/HRPC died today; J Clin Oncol, Vol. 4, No.16(June), 1999:1753-55.
(42) Dowling AJ et al.; PSA response to mitoxantrone and prednisone in 133 pts. with symptomatic HRPC; ASCO 1999 # 1298.
(43) http://pharminfo.com/pubs/msb/prostate2.html --7/30/00
(44) http://intouch.cancernetwork.com/journals/oncology/o0006a.htm
(45) Smith IE et al.; low-dose oral fluorourcil with eniluracil as first-line chemotherapy against advanced BCa; a PH II study of mitoxantrone/low-dose prednisone vs. low-dose prednisone in pts. w/asymptomatic HRPC; ASCO 2000 # 1321.
(47) Davis ID et al.; PH II study of oral eniluracil/fluorouracil in the palliatin of HRPC; ASCO 2000 # 1456.
(48) Scilsky RL; Pharmacology and clinical status of capcitabine; Oncology (Huntingt) 2000 Sep;14(9):1297-306.
(51) Kim T et al.; A PH I trial of capecitabine and cisplatin in previously untreated ACG; ASCO 2001 # 662.
(52) Watanabe T et al.; A multicenter PH II trial of Xeloda in pts. with docetaxel-refactory AMBCa; ASCO 2001 # 1991.
(53) Jacob A et al.; A PH II study of capecitabine who relapsed after HD chemo followed by peripheral bolld stem cell t’plantation for MBCa; ASCO 2001 # 1966.
(54) Kusama M et al.; A PH II study of Xeloda in pts. w/AMBCa; ASCO 2001 # 1924.
(55) Thuss-Patience PC et al.; Capecitabine: a new standard in MBCa recurring after anthracycline and taxane containing chemo; ASCO 2001 # 2012.
(56) Welt A et al.; PH I study of capecitabine and vinorelbine in preTXd pts. w/MBCa; ASCO 2001 # 1979.
(57) Tonkin K et al.; Preliminary results of a phase II study of weekly taxotere combined with intermittent capecitabine for pts. w/anthracycline preTXd MBCa; ASCO 2016.
(63) Vicaro G et al.; Vinorelbine + estramustine in HRPC; ASCO 2000 # 1436.
(64) Garcia PB; PH II study of Vonorelbin + E in the TX of HRPC; ASCO 2000 # 1480.
(66) Sweeney C et al.; Phase II study of vinerolbine + Emcyt for HRPC; ASCO 2000 # 1317.
(69) Pienta SK et al.; A PH II trial of oral estramustine and oral etoposide in HRPC; Urology 1997 Sep;50(3):401-6.
(71) Cruciani G et al.; PH II oral estramustine and oral eposibide in HRPC; ASCO 1998 # 1268.
(74) Hudes G et al.; PH II trial of vinblastine vs. vinblastine + estramustine for MHRPC; ASCO 1997 # 1127.
(75) Trudeau MG et al.; Goserlin, Estramustine, and Vinblastine combination therapy is highly effective and well-tolerated in newly DXd metastatic PCa; ASCO 2001 # 2365.