

**Conquering/Controlling/Taming
Advanced Prostate Cancer
and
Proving how to Successfully Live with
Advanced Prostate Cancer**

“Dr. Bob” Leibowitz

Compassionate Oncology Medical Group

March 27, 2007

AN
EXPERT



IS A
FAST-
TALKING
S.O.B.
FROM
OUT OF
TOWN.

-DUKE COZART,
MECHANIC
TRES PIEDRAS, NM

“The more I learn about prostate cancer, the less sure I am about what I used to know about prostate cancer.”

-Dr. Bob, circa 1994

Living Successfully with “Incurable” CaP - 1

- When CaP has spread (metastasized) to distant sites such as bones, it is not a curable disease.
- Recognizing that your disease is not curable is the most difficult concept for a patient to accept. Usually Pts. believe that if you have metastatic incurable cancer, you will probably only live a few months to one or two years. Fortunately, almost without exception, our Pts. will live much, much longer (assuming they allow us to treat them and that they actually take their medications).

Living Successfully with “Incurable” CaP - 2

For men with met. CaP, our goal is to control it:
to turn CaP into a chronic illness like diabetes or
hypertension, that you can live with and die **with** –
not die **from**.

Like diabetes or hypertension, you will need to take certain
medicines every day in order to control CaP.

TRT Case Reports: John H. – 1

John H.

11/03: 61 years old
PSA 3346
gl. 4+4/8 @ John Hopkins Hospital, 7/9 cores
Multiple bone metastasis

TRT Case Reports: John H. – 2

John H.: 11/03 Bone Scan Results

Metastasis in:

- ribs bilaterally
- T-spine
- large areas L-spine
- pelvis bilaterally
- proximal femurs
- Left scapula
- marked increased uptake T-C jct.
- upper cx. spine
- multiple areas of sternum

TRT Case Reports: John H. – 3

John H.

11/03 (cont.): 22 lb. weight loss; severe bone pain; urinates every 20 mins.

He was told to get his affairs in order because it was unlikely that he would survive more than a few months.

12/03: Treated with 13 months Triple Hormone Blockade®
Taxotere/Emcyt/Carboplatin chemotherapy x 15 doses
(thru 4/04)

09/04: PSA = 0.003; Add anti-angiogenic cocktail

1/05: Stop hormone blockade; continue cocktail
Add high dose testosterone

TRT Case Reports: John H. – 4

John H.

	3/05	6/05	7/05	8/4/05	8/18/05	11/05
T	1612	1640	3703	3831	5488	3546
PSA	0.128	0.163	0.372	0.453	0.454	0.360

	12/05	1/06	4/06	5/06	6/06	7/06
T	1644	1873	2255	4036	2324	1247
PSA	0.420	0.360	0.330	0.380	0.628	0.501

	8/06	10/06	12/06	1/07	3/8/07	3/22/07
T	2246	>1500	1159	1886	1254	2116
PSA	0.513	0.590	0.792	0.541	0.738	0.628

TRT Case Reports: John H. – 5

John H.

- 2/1/2006: Bone scan @ St. John's Hospital, Santa Monica, CA. compared to 8/18/05, showed interval improvement
- meaning less cancer
- 8/06: MRI of abd/pelvis showed probable bone mets. in lumbar spine and sacrum

TRT Case Reports: John H. – 2 Revisited

John H.: 11/03 Bone Scan Results

Metastasis in:

- ribs bilaterally
- T-spine
- large areas L-spine
- pelvis bilaterally
- proximal femurs
- Left scapula
- marked increased uptake T-C jct.
- upper cx. spine
- multiple areas of sternum

TRT Case Reports: John H. – 6

John H.

3 years and 4 months since referred to hospice and being told to get his affairs in order; to accept the inevitable; and that his life span was only 3-6 months.

03/22/2007 (2 years and 2 months after starting TRT):

PSA = 0.628; T = 2116

If this does not impress you, nothing I can ever say about treatment of prostate cancer could ever impress you.

Case Reports: Leroy T. – 1

Leroy T.

- 2/99: 81 years old; 30lb. wt. loss; severe generalized bone pain; bed-ridden
- 2/11/99: admit hospital in LA at time of bone scan; since pain required demerol
DRE → hard and nodular; PSA = 6272; PAP = 178; T = 344
gl. 4+5/9; Morphine patch
- 3/23/99: consult with Dr. Bob; 12 doses T/E/D
13 months THB[®] thru 3/00; 4 doses T/E/C
- 8/99: PSA = 18
- 2/00: PSA = 1.35 (PSA decline 99.978%)
- 12/00: PSA nadir 0.3
- 5/01: PSA = 0.33; T = 100
- 6/02 to 11/02: TRT

Case Reports: Leroy T. – 2

Leroy T. (cont.)

6/14/02: For his 85th birthday, he went out to dinner with this family.
On his next office visit, he showed us his pictures
from HOOTERS

11/02: Start HB cycle #2; Start AAC

12/03: PSA = 0.176

08/04: Last office visit

Died several months later from Alzheimer's; PSA < 10.

R.P. for Stage A CaP - 1

Non-palpable CaP found incidental to TURP

Mayo Clinic series of 148 Pts.:

- Stage A₁: low grade Gleason score and less than 1 cm³ of disease (less than 5% of TURP specimen)
- Stage A₂: more than 5% or high Gleason score

Following the TURP, you could imagine a discussion between the urologist and the Pt.

“The bad news is that some CaP was found in the prostate tissue removed by TURP.”

“But the good news – since we did not even suspect pre-op that you had CaP, if anyone could be cured, it would be you. We were lucky to discover this at such an early stage even before it caused any symptoms.”

All underwent R.P.

R.P. for Stage A CaP - 2

- Average age = 64 years old
- Mean F/U = 4.6 years
- 5 Pts. received pre-op hormone blockade
- 21 Pts.: adjuvant hormone blockade +/- R.T.
 - These Pts. were removed from the study but the 21 Pts. should have been considered R.P. failures on an intent to treat basis

R.P. for Stage A CaP - 3

Vanishing cancer syndrome (VPS)

If biopsy identifies CaP, but R.P. does not find any, urologists call this “The Vanishing Cancer Syndrome”

- Urologists appreciate this type of entity because it improves their R.P. success rates
- If there was not any cancer in the R.P. specimen, then you have a cure!!!

For Stage A₁ 8 out of 23 (25%) had VPS

For Stage A₂ 10 out of 116 (9%) had VPS

R.P. for Stage A CaP - 4

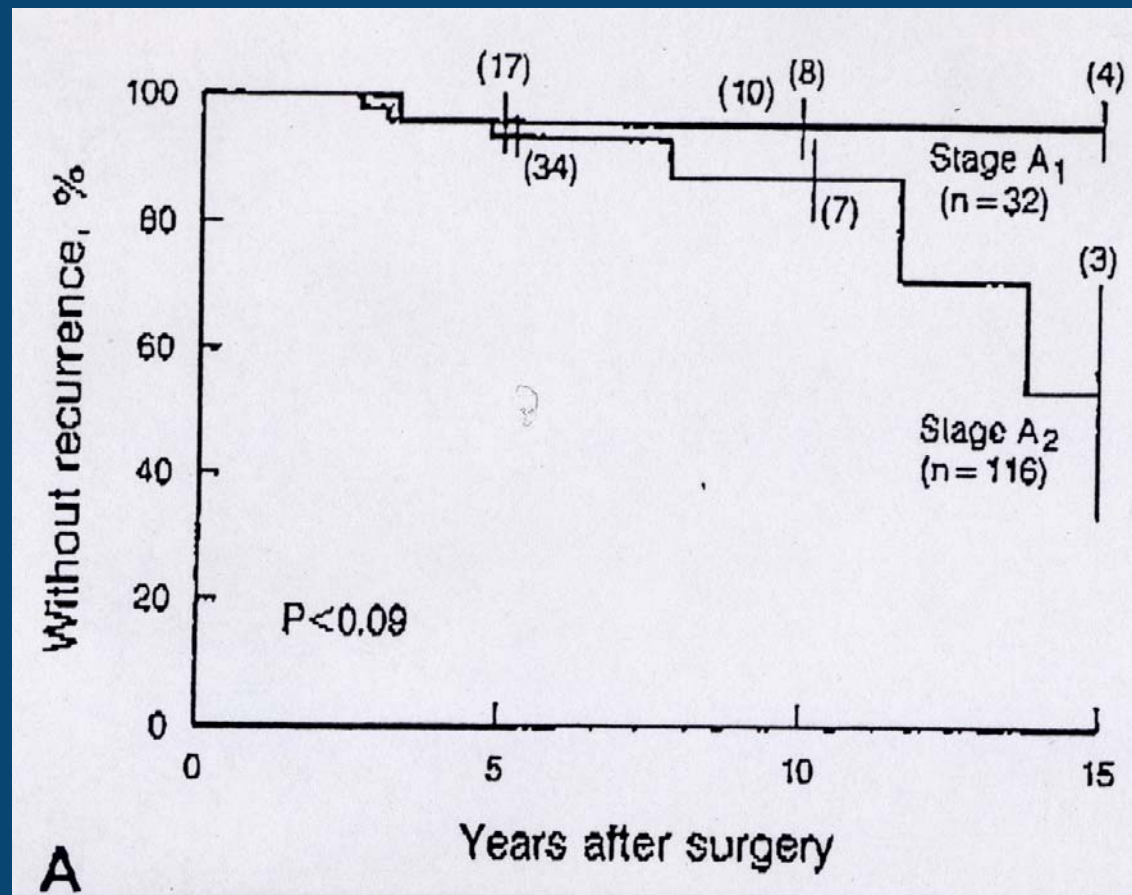
Pathology stages post-op:

Stage A₁ – 12% had Stage C or higher IIIa

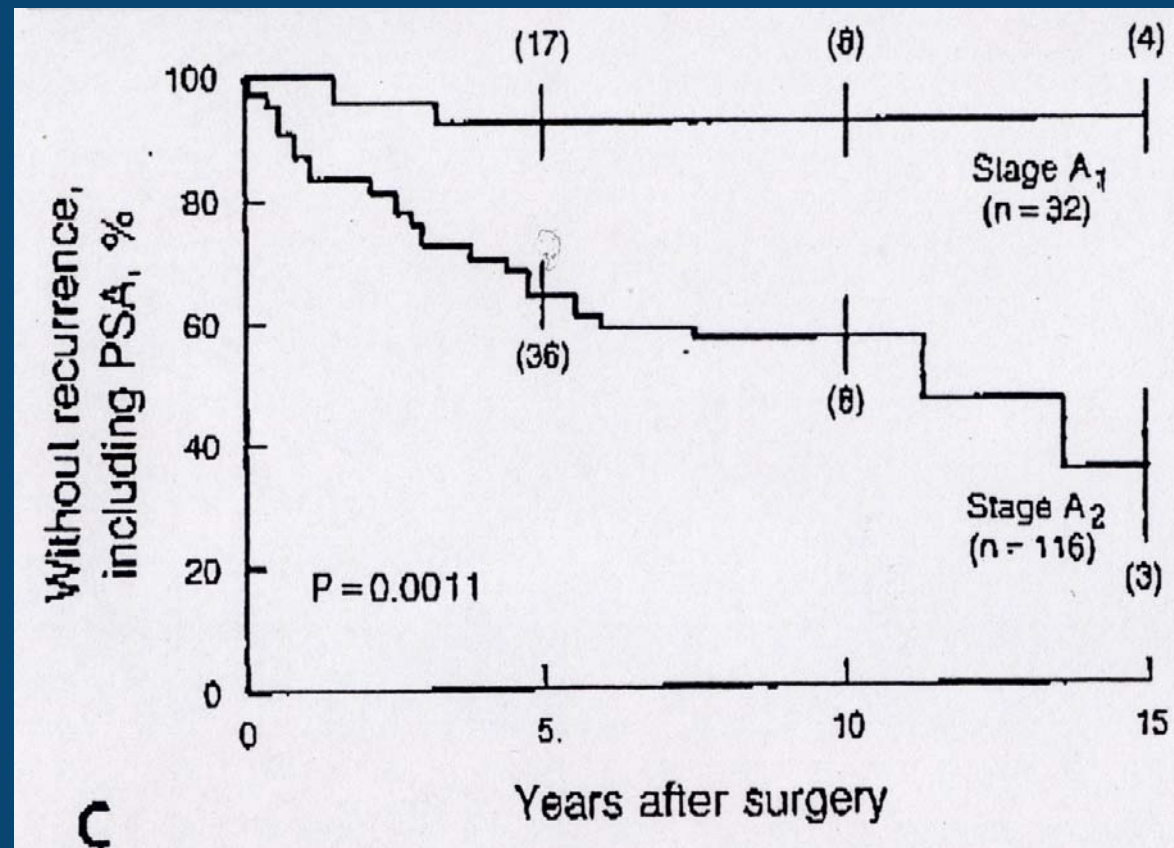
Stage A₂ - 29% had Stage C (IIIa) or higher

- 13% had residual unresectable disease left behind
- 6% had mets. to nodes
- So much for “early disease”, comments the cynical Dr. Bob

“Kaplan-Meier projections of over-all recurrence-free survival in 148 patients with clinical stage A CaP who had bilateral pelvic lymphadenectomy and R.P. (retropubic) according to clinical substage (A₁ vs. A₂)”



“Kaplan-Meier projections of over-all recurrence-free survival in 148 patients with clinical stage A CaP who had bilateral pelvic lymphadenectomy and R.P. (retropubic) according to clinical substage (A₁ vs. A₂), including PSA evaluation”



Surgical Delay and Prognosis - 1

Study looked at the interval from biopsy until R.P. to see if a delay in undergoing R.P. negatively affects prognosis.

Men grouped (in days from biopsy to R.P.):

- 60 days or less
- 61-90 days
- 91-120
- 121-150
- 151 days or greater

Surgical Delay and Prognosis - 2

Results:

- There was no negative impact on long term PSA control for any group, up through a 150 day delay
- There was not any difference in cancer control or PSA results for any of the 1st 4 groups
- Only a delay of 150 or more days resulted in a statistically significant difference in long term cancer control

Surgical Delay and Prognosis - 3

“In fact, our results showed that men who experienced surgery beyond 150 days from diagnosis actually had **BETTER** long-term cancer control rates.”

Obvious conclusion reached by Dr. Bob:

the result of this article should prevent any CaP PT from allowing a urologist to “Rush to Judgment” and frighten you into an immediate R.P.

Radical Prostatectomy and Side Effects - 1

From an admit note from 11/04:

PT understands the risks of R.P. including bleeding, infection, etc. and the potential side effects of incontinence and what seemed to me a new side effect...

Radical Prostatectomy and Side Effects - 2

...Incompetence!!!

For those post-R.P. men with any memory problems, you now know the cause.

Gotta U & Kidding Tobe. Journal of Mishugas. 2008: 18(360); 18-18.5

Only One Afraid

Dr. Peter Carroll, head of Urology at UCSF and Associate Editor of the Journal of Urology wrote an editorial for volume 173, pp. 1061-1062 in April 2005 titled,

“Early Stage CaP – Do we have a problem with over-detection, over-treatment, or both?”

Wow!! Finally, the pendulum was moving in a very positive direction

Editorial by Dr. Peter Carroll - 1

He summarized recent literature and strongly suggested that many of today's CaP patients are candidates for active surveillance and could postpone and hopefully avoid R.P. or other local therapies without significantly affecting cure rates.

Editorial by Dr. Peter Carroll - 2

“The field of urology will be judged on how we treat CaP now and in the future.”

He cautioned that if urologists do not recognize the problems of over-detection and over-treatment and deal with the issues, then a government agency or another specialty will deal with the problems instead of urologists.

Editorial by Dr. Peter Carroll - 3

We need to begin by unlinking detection and treatment since they are separate processes.

“We should identify a future path that is evidence based.”

“If that path leads to an end where we treat fewer patients, we should pursue it with energy and confidence.”

Dr. Bob can only add:

“Amen!”

Triple Hormone Blockade[®] Followed by Finasteride Maintenance[®] Therapy

In September 1991, I began to use PADT to treat patients presenting with clinically localized CaP who wished to avoid radical local therapies.

Triple Hormone Blockade[®]

THB[®] consists of 13 months of treatment with:

LH-RH agonist

- Leuprolide depot
- Goserelin depot
- Triptorelin depot
- Other competitors

Anti-Androgen (AA)

- Bicalutamide 150mg QD for everyone with coverage, samples and/or rich, generous uncles
- Flutamide 250mg, 3/d for everyone else

Finasteride 5mg maintenance[®]

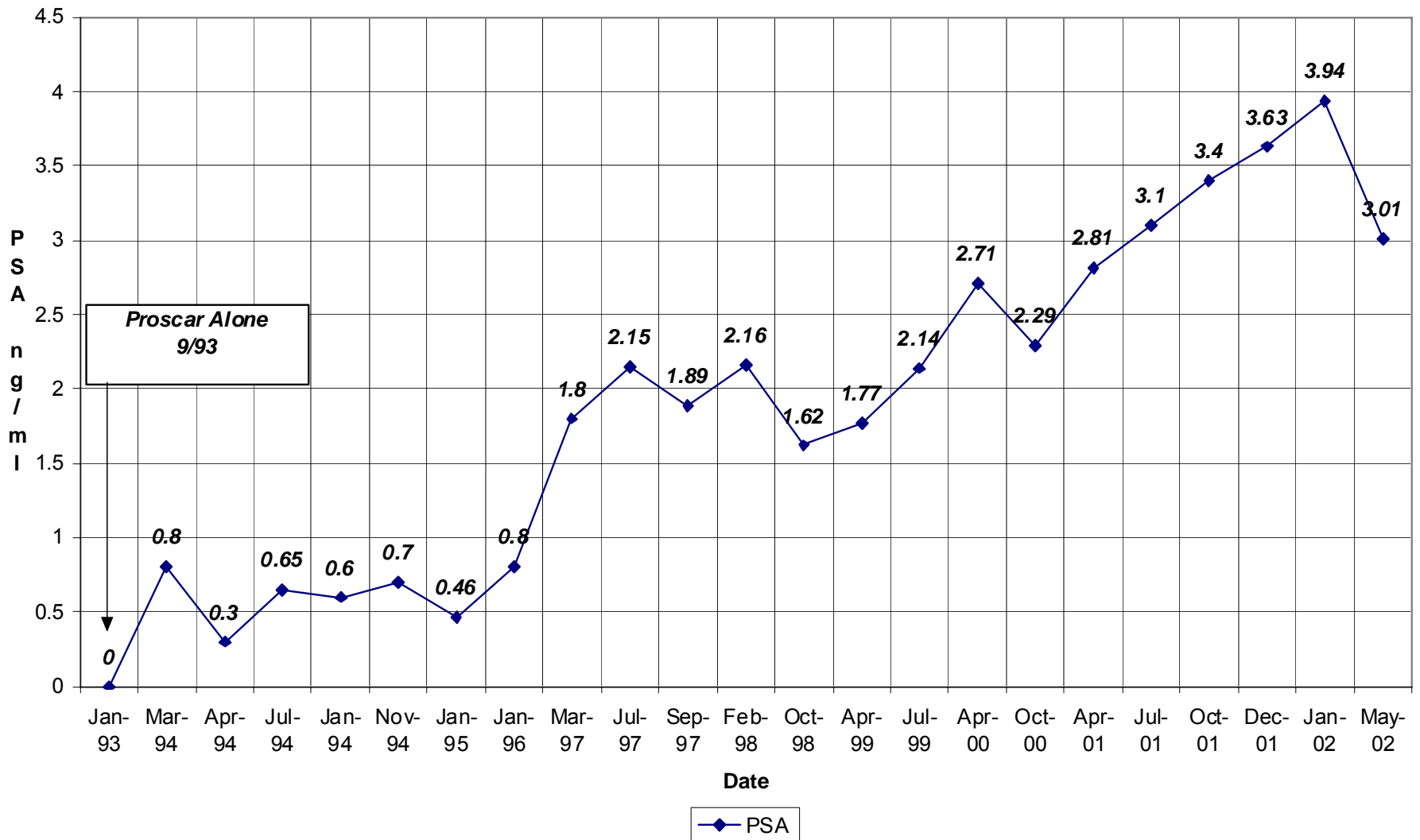
- After 13 months we stop LH-RH and AA

Number of histological foci of cancer				
Age and Race	Total No. Prostates	Single Foci	Multiple Foci	Total No. Prostates with Ca (%)
30-39 yrs.:				
Black Pts.	22	5	3	8 (25)
White Pts.	23	5	2	7 (30)
Totals	55	10	5	15 (27)
40-49 yrs.:				
Black Pts.	28	2	8	10 (35)
White Pts.	22	6	1	7 (32)
Totals	50	8	9	17 (34)

Table adapted from Sakr W A et al. Journal of Urology. 1993; 150: 379-385

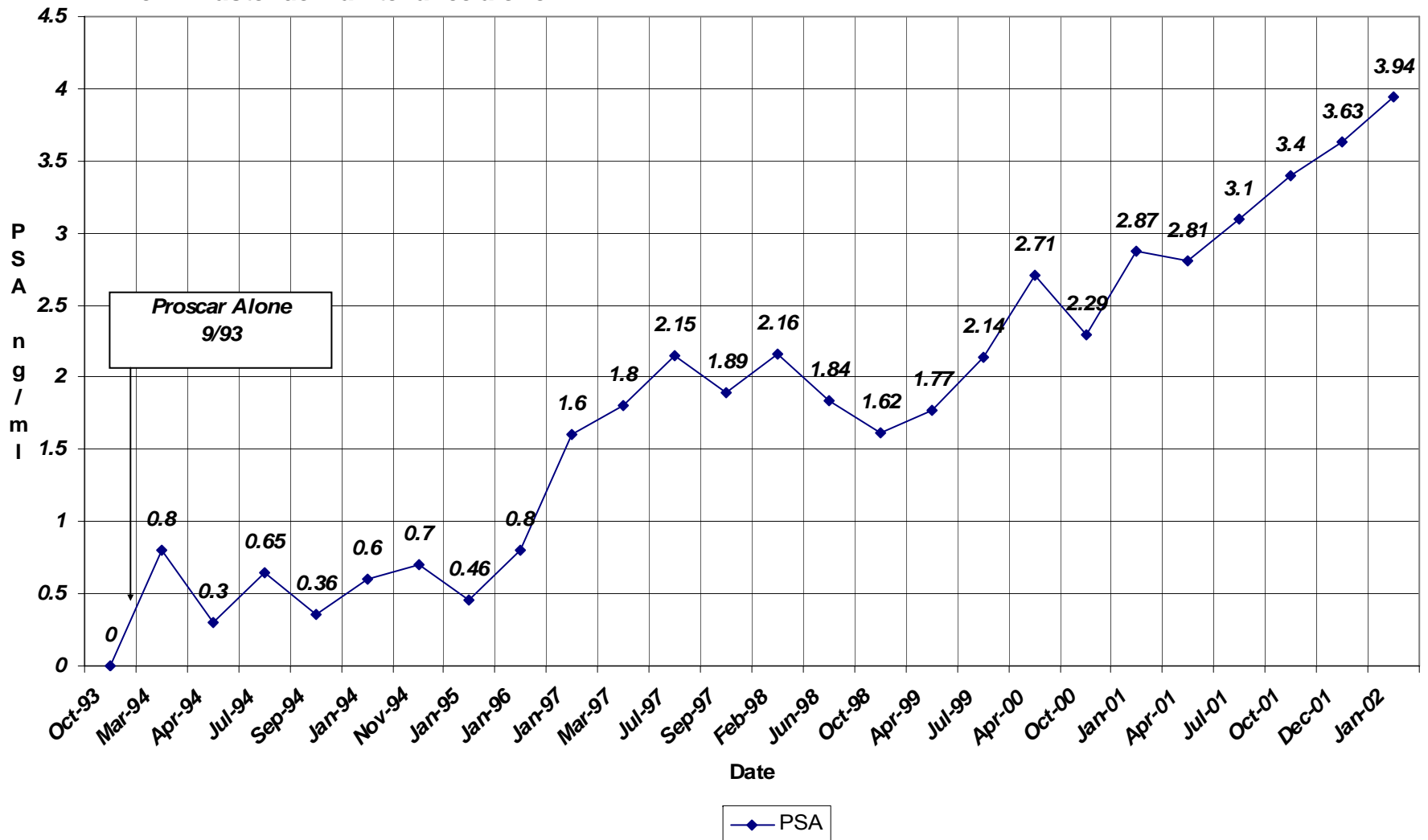
76 y/o Gleason 3+3/6 PSA 34
 TAB Started 9/91 for 24 months
 PAP elevated Stage D-0

Case Reports: Max K. - 1



76 y/o Gleason 3+3/6 PSA 34
 Elevated PAP x 2 Do
 TAB Started 9/91 for 24 months
 Then Finasteride Maintenance alone

Case Reports: Max K. - 2



Case Reports: Max K. - 3

Date	PSA	Date	PSA
August '02	3.64	November '05	6.75
November '02	3.09	April '06	7.01
June '03	3.62	June '06	7.27
September '03	3.8	December '06	6.45
December '03	5.6	January '07	6.2
June '04	4.58		
September '04	4.97		
November '04	5.15		
February '05	4.79		

Case Reports: Max K. - 4

As of March 27, 2007, it has been over 15 ½ years since his high risk presentation with a PSA 34, Stage D₀ because of elevated and confirmed PAP.

Never received any local treatment; 1 cycle THB since 9/93, over 13 ½ years

His only CaP treatment has been Proscar 5 mg. once each day; so called Finasteride Maintenance[®] Therapy.

In just a few months, Max will celebrate his 92nd birthday.

He still golfs several times a week at El Cab.

Primary Androgen Deprivation Therapy (PADT)

Hormone therapy for CaP – is cure possible after all?

Conclusion: The role of hormone blockade as the first treatment of early CaP should be readdressed in controlled studies

TRT Case Reports: Stuart B. – 1

Stuart B.

- 12/95: 52 years old; gl 3+3/6 at JHH; PSA = 7.3
5 mos. 2-drug hormone blockade
Then 9 mos. Triple Hormone Blockade®, then Proscar alone.
- 7/03: Started high dose TRT; later added in some anti-angiogenic cocktail

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

® Triple hormone blockade, triple androgen blockade, and finasteride maintenance are the registered trademarks of Robert L. Leibowitz, M.D.

TRT Case Reports: Stuart B. – 2

Stuart B. (cont.)

	9/03	11/03	1/04	3/04	5/04	7/04
T	1498	1545	1539	2062	1043	3678
PSA	8.11	5.7	7.1	5.6	8.35	7.32 ↑

thalidomide 50mg added

	9/04	11/04	1/05	3/05	4/05	6/05
T	1540	2674	1214	1286	2237	1232
PSA	8.66	8.59	7	7.12	6.4	7.57

	8/05	11/05	12/05	1/06	2/06	3/06
T	2068	1427	1474	2212	3181	2791
PSA	9.19	9.01	11.1 ↑	11.5	9.25 ↑	6.92

Leukine added

thalidomide stopped; Revlimid 5mg/day started

	4/06	5/06	6/06
T	2059	1599	1863
PSA	7.8	7.62	6.99

TRT Case Reports: Stuart B. – 3

Stuart B. (cont.)

11 years after diagnosis of CaP:
no local treatment, 1 cycle of HB and 3 years of high dose TRT

Expired 6/06



Glenoaks Pathology Medical Group, Inc.

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PHONE (800) 620-4644 – FAX (800) 970-4644 – E-MAIL POSEY@VEL.NET

AUTOPSY REPORT APS-P057-06

RE: STUART W. B

CONCLUSION AND OPINION: Based on these autopsy findings and the clinical information available to me, in my opinion, Stuart W. B, a (died as a result of severe coronary artery insufficiency due to hyper atherosclerotic cardiovascular disease complicated by sudden irreversible (clinical heart attack).

Coronary artery atherosclerosis can be compared to rusting of an iron pipe. Over years, the lumen becomes slowly narrowed and can become completely occluded by slowly narrowing the normal blood vessel lumina, resulting in greatly reduced oxygenated blood flow to the heart muscle (myocardium). When this damage can occur, causing an acute myocardial infarct, or the heart can stop, placing the heart at great risk for an irreversible, fatal cardiac arrhythmia (clinical heart attack).

In this case, Mr. B had 90% and 85% luminal compromise of the right and left coronary artery systems, resulting in greatly reduced oxygenated blood flow to the heart muscle (myocardium), and this in concert with hypertension placed him at great risk for a sudden, irreversible, fatal cardiac arrhythmia or clinical heart attack.

Mr. B was diagnosed with moderately differentiated adenocarcinoma of the prostate gland circa 1996 and he has been under treatment since that time. At autopsy, there is no evidence of recurrent or residual tumor. The prostate gland demonstrates only benign stromal and glandular hyperplasia with no evidence of malignant tumor.

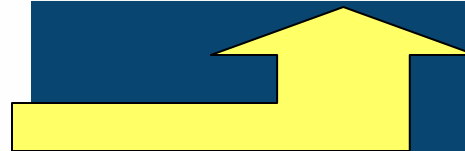
The postmortem toxicology findings on the comprehensive blood screen are positive only for ethanol, and this is attributed to postmortem decomposition and does not suggest that he ingested alcohol prior to his death. Please see the attached toxicology report outlining the comprehensive blood screen. There are no assays for many of the drugs prescribed for Mr. B, although the manufacturer of the medication may have an assay for a specific medication, but they are not available for commercial use.

CAUSE OF DEATH: Severe coronary artery insufficiency due to hypertensive and occlusive atherosclerotic cardiovascular disease complicated by sudden irreversible cardiac arrhythmia (clinical heart attack).

MANNER OF DEATH: Natural.

TRT Case Reports: Stuart B. – 4

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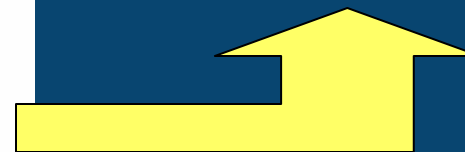
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TRT Case Reports

How many times have you heard that:

- 1) Hormone blockade cannot cure anyone with prostate cancer.
- 2) Giving T to someone with prostate cancer is like pouring gasoline on a fire.

HRPC Definitions

- Rising PSA with a castrate level of testosterone by definition is hormone refractory prostate cancer (HRPC)
- A more appropriate term should be hormone resistant CaP because with the use of secondary hormone blockade, the PSA may again decline

Treatment Options for HRPC - 1

If on Combined Androgen Blockade (e.g. Lupron and Casodex or other AA) and PSA is rising, you must stop the Casodex (or AA) because of:

“The Benedict Arnold Syndrome”

Benedict Arnold Syndrome - 1

Initially AA bind to androgen receptors and block the ability of androgens to stimulate CaP cells to grow (antagonist effect)

Benedict Arnold Syndrome - 2

- However, over time, mutations in the androgen receptors develop; there may be amplification of AR
- “Things” (ligands) other than androgen may stimulate androgen receptors
- Other mechanisms result in AA stimulating CaP cells to grow (agonist effect rather than antagonist)

Treatment Options for HRPC - 2

- Most so-called experts advise using sequential endocrine therapies
- Some advocate using a second and even a third AA after progression on prior AA
- You also have the option to increase dose of Casodex to 150-200mg per day

Treatment Options for HRPC - 3: Endocrine

Although it seems that there are numerous secondary hormone blockade treatment options:

1. None has been found to prolong life
2. The average response rate is about 35%
3. The average duration of response is 3-4 months

Toxicities Brachytherapy (seeds) vs. R.P.

From 3/01 to 6/02, 435 Pts.; average F/U 24 mos.

Side Effects	Seeds (308 Pts.)	R.P. (127 Pts.)
↑ urinary urgency	38%	26.5%
urinary pain	19%	2.1%
↑ daytime frequency	37%	16%
↑ nocturnal frequency	31%	14%
urinary incontinence	20%	49%

Toxicities: Seeds vs. R.P.

Side Effects	Seeds (308 Pts.)	R.P. (127 Pts.)
↑ fecal incontinence	9%	2%
↑ rectal bleeding	15%	none
reduced erectile function	46%	83.3%

Recurrent Disease – 1

What is the definition of PSA failure after radical prostatectomy?

- In the medical literature, there are 55 different definitions!!
- After failed R.T., there are 99 different definitions of PSA failure!!

Recurrent Disease - 2

More than 10 years ago, I wrote that if the first attempt to cure you with radical local therapy was not successful, then it is extremely unlikely that another form of radical local therapy will cure you, but very likely that it would result in very significant side effects that would likely be permanent.

Radiotherapy After Radical Prostatectomy - 1

- 69 Pts. were treated with curative intent R.T. at a median of 16 months after R.P. for a rising PSA
- Within 5 years of R.P., about 25% of men will be treated with R.T., according to medical literature
- The Pts. in this study are from the CaP-SURE database

Radiotherapy After Radical Prostatectomy - 2

- Sexual and bowel functions were markedly worse in men who were treated with “salvage” R.T. than those treated “only” with R.P.
- Only 3% of men were able to achieve an erection firm enough for intercourse
- Only 39% were continent

Radiotherapy After Radical Prostatectomy - 3

Conclusion:

Given the unclear survival benefits men must consider that salvage R.T. adversely affects sexual, urinary and bowel function

(Dr. Bob adds that to date, salvage R.T. has not been found to prolong overall survival but clearly adversely affects your **quality of life**)

Recurrent Disease - 3

This 2007 Mayo Clinic article states that “a small fraction of these men may have a local disease recurrence only.”

“The reality is that they have micrometastatic disease that will not respond to local measures.”

CaP cells had spread before (or during) local therapy and are producing PSA. Unfortunately our scans can not identify the sites of metastatic disease

Recurrent Disease - 4

The authors correctly point out that if distant disease is present, local treatment will not improve survival (and in my opinion, may shorten it). Unfortunately, side effects occur whether the PSA goes up or down or remains stable.

Adjuvant R.T. After R.P.

- Meta-analysis of all randomized clinical trials comparing immediate post-op R.T. for Pts. with positive margin or pathologic T₃ vs. observation with delayed R.T. for a rising PSA
- No difference in overall survival

Conclusion: To date, adjuvant R.T. has not been shown to improve overall survival compared to observation

R.T. Results

203 T₁₋₄ Pts.

No non-metastatic CaP Pts.

Treatment with R.T. alone

All had surgical staging

F/U of 10 years

81% locally advanced

Results:

- b PFS 45%
- Daily use of pads for urinary leakage 22%
- Daily use of pads for fecal leakage 16%
- Significant impairment of sexual function

“You are entitled to your own opinion, you are not entitled to your own facts.”

R. T. for HRPC: Clinically Localized - 1

- Median age = 72; PSA = 7.4; R.T. median dose = 70 Gy.
- F/U from initial diagnosis 68 mos; since R.T. 33 mos.
- 5 out of 29 did not have rising PSA after R.T. – 2 died of unrelated causes
- Only 3 out of 29 remain alive without evidence of CaP recurrence

R. T. for HRPC: Clinically Localized - 2

- 24 out of 29 Pts. developed a “biochemical failure” after a median of 9.2 mos. from R.T.
- 23 out of 24 developed overt clinical disease after median of 7.1 mos
- Only 1 of 24 Pts. with “biochemical failure” has not yet developed obvious mets.
 - He has only 1 month F/U since rising PSA
- Only 5 of 23 Pts. with clinical failure are alive

R. T. for HRPC: Clinically Localized - 3

- All Pts. with pre-R.T. PSA values over 20 failed distantly
- In an M.D. Anderson series of 29 Pts. treated with R.T. after 38 mos. of HB, the four year actuarial DFS rate was 20%
- Our experience shows that despite R.T. for localized HRPC, prognosis is DISMAL
- 5 year survival from R.T. is 28% and only about ¼ of Pts. are free of disease or PSA progression at 5 years

HRPC Radical Treatment Option - 1

Exenterative salvage

Surgery for HRPC – not recommended by Dr. Bob

Study:

- 21 Pts., age 60, PSA = 30
- Time since primary treatment = 82 months
- Planned surgery cystoprostatectomy (CP)
- ileal conduit or continent urinary reservoir

Results:

5 of 21 Pts. had total pelvic exenteration which means they required colostomy in addition to CP

HRPC Radical Treatment Option - 2

Results (continued):

- 8 of 21 significant post-op complications
- F/U 20 months – PSA nadir 1.85
- Median overall survival – 12.4 months

Conclusion by authors:

CP should be recognized as a reasonable palliative approach

Conclusion by Dr. Bob:

Say, what?

My momma didn't raise any foolish children.

“Everyone is entitled to their own opinion, their own **WRONG** opinion.”

-Dr. Bob, circa 1993

CaP Chemotherapy Benefits - 1

- Chemotherapy for CaP through the early 1990's was usually considered as too toxic and not very effective
- In 1996, Tannock reported on a study comparing prednisone alone to prednisone plus mitoxantrone (M)

CaP Chemotherapy Benefits - 2

- There was no survival advantage for mitoxantrone (M) but Pts. on M had an improved quality of life and better pain control than predisone alone
- I stopped using M in 1994

CaP Chemotherapy Benefits - 3

- Taxotere received FDA approval to treat met. HRPC in 5/2004
- In 6/2004, 2 studies were reported at the American Society of Clinical Oncology (ASCO) Plenary Session comparing Taxotere to M
- Dr. Bob first began using Taxotere protocols for all CaP Pts. requiring chemotherapy in the summer of 1997!!!

CaP Chemotherapy Benefits – 4

Taxotere improved the median survival in the 2 studies by:

- a. 2 mos.
- b. 5.6 mos.
- c. 9.1 mos.
- d. Almost 15 mos.
- e. No prolongation in survival

CaP Chemotherapy Benefits – 4

Taxotere improved the median survival in the 2 studies by:

Answer:

a. 2 months

HRPC: Taxotere

The two Taxotere trials that led to FDA approval of Taxotere to treat patients with metastatic HRPC found that:

- only about 1/3 of Pts. respond
- the median survival advantage was 1.9 mos. in 1 study and 2.4 mos. in the other

COMG Protocol Validations: Taxol/C/E

- In the summer of 1997, I started to treat all CaP Pts. requiring chemotherapy with Taxotere/Emcyt.
- After their PSA plateaued, I added carboplatin
- When each of the first 4 or 5 Pts. responded to carboplatin, I changed the protocol to T/E/C

HRPC Weekly T/E/D +/- Carboplatin (9/99)

Patient's Initials	Age	Initial PSA	End PSA	Doses T/E/D	Date Started	Date Stopped	# of Months on Treatment	# Doses w/Carbo	% Decline	# of Prior Hormone Regimens	Most Recent PSA
JK	59	36.65	3.11	22	Apr-98	Sep-98	6	14	91.5%	6	8.90
RR	63	31.5	3.13	21	May-98	Sep-98	5	9	90.1%	3	1.99
RN	76	228	10.65	17	Apr-98	Aug-98	5	5	95.3%	4	16.00
RB	66	15.8	13.55	19	Apr-98	Oct-98	7	7	14.2%	4	26.67
EK	76	77	2.60	20	Jan-98	Jul-98	6	0	96.6%	4	85.90
SM	79	15.5	7.31	17	Apr-98	Sep-98	5	9	52.8%	3	86.00
TI	71	120	2.98	22	Apr-98	Aug-98	5	8	97.5%	3	0.62
KR	69	16.28	1.53	11	Jan-98	Apr-98	3	0	90.6%	3	0.15
CFH	59	0.84	0.34	12	Mar-98	May-98	2	0	59.5%	2	39.80
AP	69	239	7.01	48	Sep-97	Oct-98	13	15	97.1%	3	47.53
JP	58	13.42	0.04	14	Jul-98	Nov-98	5	5	99.7%	3	0.26
CR	74	2.54	0.66	14	Jul-98	Oct-98	4	0	74.0%	3	2.10
DM	73	53.8	5.20	16	Jul-98	Oct-98	4	15	90.3%	3	1.05
LB	69	25.87	1.50	16	Aug-98	Dec-98	4	8	94.2%	3	0.97
NS	55	4.58	5.80	6	Oct-98	Dec-98	2	2	0%	2	14.97

HRPC Weekly T/E/D +/- Carboplatin (9/99)

Analysis

Mean PSA for patients off treatment	4.36
% of patients with $\geq 50\%$ decline	76.5%
% of patients with $\geq 90\%$ decline	58.8%

COMG Protocol Validation

Study:

- Meta-analysis of metastatic HRPC Pts.
- chemotherapy +/- Emcyt
- 5 randomized trials

Results:

Adding Emcyt to chemotherapy significantly improves both time to tumor progression and overall survival compared to chemotherapy alone

HRPC: Taxotere plus Thalidomide

Randomized study:

Taxotere alone vs. Taxotere + Thalidomide

	Taxotere Alone	Taxotere + Thalidomide
Response rate	37%	53%
Survival	14.7 mos.	25.9 mos.
PFS	3.7 mos.	5.9 mos.

Intermittent chemotherapy: Dr. Bob's "Pearls"

- Never set an arbitrary PSA level to start another cycle of chemotherapy and/or hormone blockade
- If a PT was responding to treatment when chemotherapy was stopped and remains off chemotherapy for 1 year or more, then retreatment with that same chemotherapy is almost always successful
- Thus, it is important to try to stop chemotherapy while it is still effective:
 - for most Pts., I use 15 doses of T/E/C
 - for perhaps 3% of Pts. with met. disease, I might give 18 doses and rarely up to 21 doses

Intermittent chemotherapy: COMG Successful Approaches

- While on chemotherapy and hormone blockade, Pts. are also being treated with my CaP Anti-angiogenic Cocktail (AAC)
- When chemotherapy has been completed, AAC and HB continue
- When HB has been completed, men are maintained on AAC
- Pts. may elect to discuss the risks, benefits and alternatives for adding in high dose TRT after completing HB

Intermittent Chemotherapy

After restarting chemotherapy:

- 50% of Pts. had $\geq 50\%$ decrease in PSA
- 35% had stable PSA
- 15% had PD

Results: COMG Calcitriol – Us vs. Them

	Us	Them
Deaths	1-2% and F/U over 5 years	49% and F/U 16.4 months
Side effects leading to stopping treatment	0%	25%
Side effects leading to Hospitalization	0%	41% vs. 27% (placebo) (DN-101)
% on intermittent chemotherapy	90%	18% vs. 20% (placebo) (DN-101)

TRT Case Reports: Richard W. – 1

Richard W.

- 2/95: 52 years old; pain in low back, legs, buttocks, and pelvis; PSA = 2378
PAP = 51.8; gl 4+4/8 all cores; marked locally advanced disease
Bone scan - multiple bone mets; C-T chest showed too numerous to
count mets in both lungs up to 1.5 cm in diameter
Start cycle #1 Triple Hormone Blockade®, lasted for 13 mos.
- 3/96: PSA = 0
- 8/97: PSA = 24; start cycle #2 hormone blockade, lasted for 11 mos.
start cycle #1 chemotherapy with 16 doses Taxotere/Emyct
- 10/00: PSA = 42; start cycle #3 hormone blockade, lasted for 11 mos.
start cycle #2 chemotherapy with 18 doses Taxotere/Emyct/Carboplatin

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at
<http://www.compassionateoncology.org/publications.html>)

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trademarks of Robert L. Leibowitz, M.D.

TRT Case Reports: Richard W. – 2

Richard W. (cont.)

- 01/02: Start anti-angiogenic cocktail
- 06/02: Start cycle #1 T, lasted for 10 mos. through 4/03
(PSA = 15, T = 500)
- 07/03: PSA = 65; start cycle #4 hormone blockade, lasted for 13 mos
Start cycle #3 chemotherapy x 10 doses (PSA = 0.06)
- 08/04: Start cycle #2 T, lasted 5 mos. until 1/05 (PSA = 49)
- 01/05: Start cycle #5 hormone blockade, lasted until 2/06 (PSA = 0.05)
- 03/1/06: Start TRT

TRT Case Reports: Richard W. – 3

Richard W. (cont.)

	3/06	4/06/06	4/18/06	5/06	6/12/06	6/22/06
T	1324	1690	1222	2288	1356	4100
PSA	1.360	4.580	5.950	3.980	4.900	3.160

	7/06	8/06	9/06	10/5/06	10/20/06
T	2319	3293	8000	5882	2313
PSA	2.300	2.310	1.160	4.500	3.940

11/06: Died of metastatic kidney cancer

Anti-angiogenic Cocktail

- Leukine (GM-CSF; sargramostim)
- Thalimid (thalidomide) / Revlimid (lenalidomide)
- Proscar (finasteride) / Avodart (dutasteride)
- Aredia (pamidronate disodium) / Zometa (zoledronic acid)
- Celebrex (celecoxib)
- LMWH (low molecular weight heparin)
- Avastin (bevacizumab)
- Cytosan (metronomic cyclophosphamide)
- alpha interferon

Anti-angiogenic Cocktail: Targeted Therapy

- Nexavar (sorafenib)
- Sutent (sunitinib)
- rapamycin (mTOR inhibitor)
- Tarceva (erlotinib)
- Herceptin (trastuzumab)
- Gleevec (imatinib mesylate)

AAC – Leukine Long Term Responders - 1

- 29 Pts. rising PSA after local therapy
- No gross mets; PSA 0.4 to 6
- Treatment with GM-CSF 250 mcg/m² days 1 to 14 of a 28 cycle
- This article reports on Pts. still in remission after 4 yrs.

AAC – Leukine Long Term Responders - 2

- In 1999, Small et al. reported on 23 Pts. with met. HRPC treated with GM-CSF
 - Median PSA decline 37%
- A second group of 13 Pts. were treated with day 1 to 14, 250 mcg/m² GM-CSF followed by 250 mcg/m² GM-CSF every M-W-F
 - All but 1 Pt. had a PSA decline, including 1 Pt. with PSA decline from 77 to 0.1 and improved bone scan

AAC – Leukine Long Term Responders - 3

- 22 of 29 Pts. considered short-term since all progressed by 33 mos.
- Median pre-PSA 3.7; nadir 3.7
- PSA Doubling Time (DT) 8.2 mos.; mean on GM. 21.1 mos.
- Therapy well tolerated.
- No long term toxicity

AAC – Leukine Long Term Responders - 4

- 7 of 29 Pts. (24%) remain in remission and free of disease at a median of 5.1 yrs. since start of GM.
- PSA: 1.5 to 0.4
- PSA DT: 9.2 mos. to more than 33 mos.
- Long-term responders tended to have more favorable baseline prognostic factors

AAC – Leukine/Thalidomide

- 18 Pts. rising PSA after local therapy - No gross mets. and No prior HB
 - Leukine 250 mcg/m² 3 days per week
 - Daily thalidomide
- 18 of 18 Pts. had PSA decline of 26% or more with a median decrease of 59%
- Conclusion: This may represent an alternative to HB

COMG Protocol Validation

Leukine plus Revlimid in HRPC

Study:

- 16 Pts. (12 with metastasis)

Results:

- 9 of 16 Pts. (56%) have PSA decline
- Study from Cleveland Clinic - they use very different dosing schedule than COMG but nice to see 56% response rate

Thalidomide plus GM-CSF - 1

Study:

22 Pts. with met. HRPC were treated with Thalidomide and GM-CSF

Results:

Just 2 weeks after treatment was started, all Pts. showed a decrease in PSA

Thalidomide plus GM-CSF - 2

Study:

18 Pts. with rising PSA after local treatment

Results:

PSA decline $\geq 48\%$ in all evaluable Pts. and median decrease is 63%

Survival for Patients Presenting with Metastatic Prostate Cancer

- No prior therapy either local or hormone blockade
- 36 prospective randomized trials comparing combined hormone blockade to Lupron alone
- Survival:
 - Lupron + placebo – 28.3 mos.
 - Lupron + flutamide – 35.6 mos.
- The maximum survival ever observed:
 - Lupron alone – 30 to 31 mos.
 - Combined hormone blockade – 35-36 mos.

Hormone Refractory Prostate Cancer (HRPC)

Randomized study

- flutamide vs. prednisone for patients who progressed on primary HB:
- no difference in
 - response rate
 - disease free survival
 - overall survival

Advanced CaP

Anti-angiogenic Cocktail

Leukine and Revlimid or Thalidomide are not chemotherapy; not hormone blockade, and they enhance your immune system.

Isn't this exactly what you have been looking for?

And if these medicines control your PSA, you avoid going back on HB.

Advanced CaP

Anti-angiogenic Cocktail

Remember, you cannot develop hormone refractory prostate cancer unless someone puts you back on HB. The longer you are off HB, the much longer you live.

TRT Case Reports: Dr. Earl S. – 1

Dr. Earl S.

05/89: 59 years old; PSA 134; gl. 7; C.T. - ECE & SV; L + KC

08/89: R.P. @ UCLA; pos. urethral margins; PNI; ECE

10/89: PSA = 0

4/92: PSA = 2.0

01/96: PSA = 6.1

05/99: Consult with Dr. Bob; PSA = 11.99; T = 228

Refused HB; Rx with finasteride, pamidronate, thalidomide

8/00: PSA nadir 4.13

6/02: TRT started; PSA = 6.86; T = 278

TRT Case Reports: Dr. Earl S. – 2

Dr. Earl S. (cont.)

	10/02	TRT Discontinued 11/21/02	TRT Restarted 2/6/03	3/03	6/03	10/03
T	714	380	2426	873	>1600	1421
PSA	11.3	15.0	12.4	13.2	12.5	13.5

	2/04	5/04	8/04	11/04	2/05	5/05
T	2345	3120	2478	1432	2280	>1600
PSA	14.1	15.2	19.0	17.4	17.0	15.0

	6/05	8/05	10/05	12/05	2/06	4/06
T	1458	1069	1458	1521	1545	2986
PSA	20.1	16.6	14.9	17.6	19.6	17.4

	7/06	10/06	1/07	2/07	3/07
T	3521	2003	1280	1676	2389
PSA	17.0	19.0	24.3	16.1	17.1

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

TRT Case Reports: Dr. Earl S. – 3

Dr. Earl S. (cont.)

4/05: Leukine added

In 05/99, PSA = 11.99; T = 228

More than 7 years later, PSA = 16; T = 1692, with marked improvement in quality of life

PSA rose less than 50% in 7 years:

From 5/99 thru 3/06, PSA increased by 1/3

PSA Doubling Time > 15 years in spite of being on TRT since 6/02

TRT Case Reports: John S. – 1

John S.

01/03: 55 years old - A.A.; PSA 7.7; gl. 3+4/7; 6/6 cores;
Endorectal MRI - ECE

03/03: R.P. @ Memorial-Sloan Kettering, 2 pos. nodes, gl. 4+4/8;
SV. pos. margins; ECE; 2500cc EBL

07/03: PSA unmeasurable

04/04: PSA = 0.7

12/03: PSA = 0.23

06/14/04: PSA = 1.02

01/04: PSA = 0.35

08/4/04: PSA = 1.98; PSA DT = 2 mos.; T = 334; PAP = 0.15

Rx 13 mos THB[®] (KC/HC), plus 15 doses T/E/C; AAC added as tolerated

8/05: Discontinued HB; continue AAC and added high dose TRT

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TRT Case Reports: John S. – 2

John S.

	9/05	10/05	11/05	12/05	1/06	2/06
T	4064	3961	4421	2620	2433	2406
PSA	<.01	<.01	<.01	<.01	<.01	<.01

	3/06	4/06	5/06	6/06	2/07
T	2901	2921	2815	1708	2691
PSA	<.01	<.01	<.01	<.01	<0.01

Case Reports: Dr. Joe S. – 1

Dr. Joe S.

05/98: 69 years old; PSA = 3.97 (but on P so corrected is 7.94)
T_{2A}; gl. 3 + 3/6; 1% of 1/6 cores
Father got CaP at age 70 and died of met. CaP at age 75
1 brother age 66 – CaP and had R.P. but died of
mets. 2 yrs. later
2 paternal uncles with CaP in their 70's; 1 died from mets.
Start cycle #1 HB + L + 3C + P x 13 months (until 7/99)

11/99: PSA = 0.26; T = 342

11/00: PSA = 1.69

07/01: PSA = 2.54; T = 566

11/01: PSA = 3.82

02/02: PSA = 2.39

11/02: PSA = 4.71; original
slides reviewed by J.H.H.
– no CaP

02/03: PSA = 7.14; T = 751

03/4/03: PSA = 9.2; C-T and bone scan – sclerotic areas sacrum, Left iliac,
L₄ and L₅; biopsy gl. 4+4/8 1/8 cores

Case Reports: Dr. Joe S. – 2

Dr. Joe S.

- 03/21/03: Start cycle #2 HB; no anti-androgen; use A/G HC; PSA = 11.9
Taxotere/Emcyt/Carboplatin chemotherapy x 13 doses
- 06/03: PSA = 0.231
- 10/03: PSA = 0.035
- 01/04: PSA = 0.009
- 05/04: Discontinue HB
- 09/04: PSA = 0.071; T = 330
- 01/05: PSA = 1.21; T = 308
- 06/05: PSA = 3.11
- 08/05: PSA = 3.85
- 12/14/05: Re-consult with Dr. Bob; PSA = 9.28; T = 389
Start anti-angiogenic cocktail

Case Reports: Dr. Joe S. – 3

Dr. Joe S.

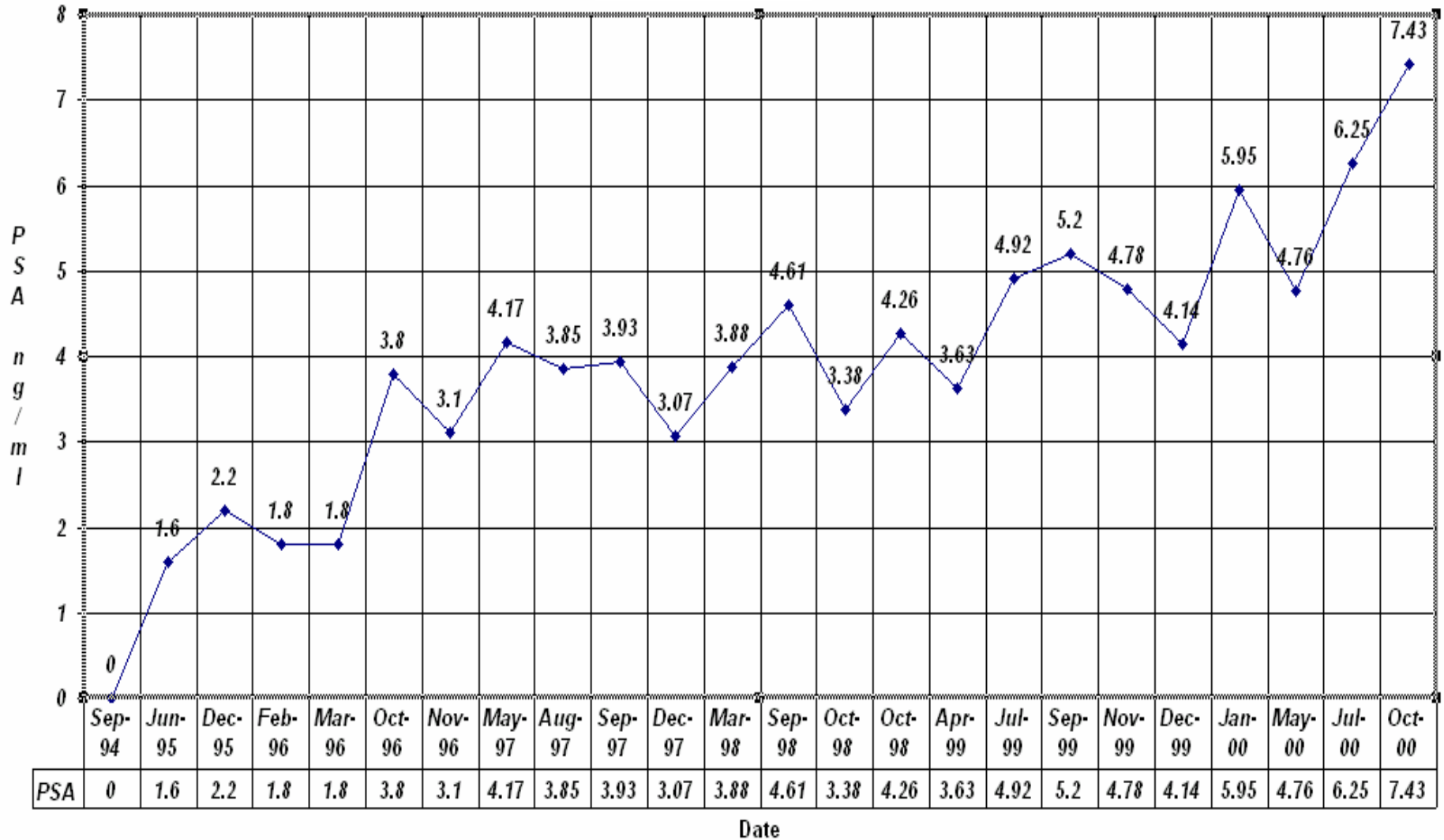
12/28/05: PSA = 3.49
02/08/06: PSA = 4.78 (was off thalidomide)
03/21/06: PSA = 3.61
05/17/06: PSA = 2.39
08/08/06: PSA = 1.79
10/04/06: PSA = 1.46; T = 244
01/19/07: PSA = 1.46
03/21/07: PSA = 1.59; T = 252

57 y/o 9/93 gl 7

PSA = 4.8

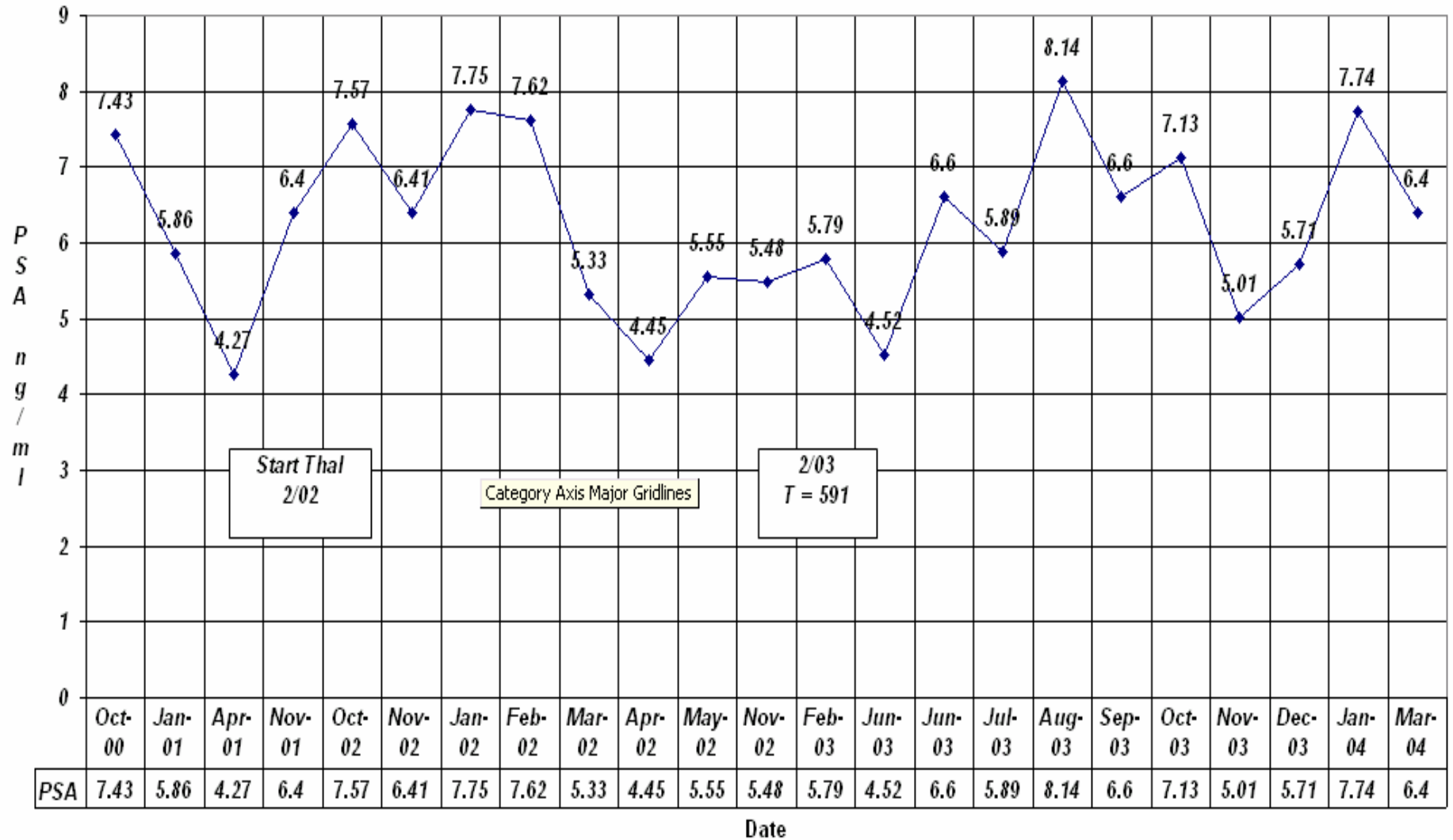
TAB x 13 mos end 10/94

Case Reports: BFO - 1



57 y/o 9/93 gl 7
 PSA = 4.8
 TAB x 13 mos end 10/94

Case Reports: BFO - 2



Case Reports: BFO - 3

Date	PSA
April '04	6.83
May '04	9.76
June '04	9.23, start GM-CSF
July '04	6.87

Case Reports: BFO - 4

<u>8/04</u>	<u>10/04</u>	<u>11/04</u>	<u>1/05</u>	<u>2/05</u>	<u>3/05</u>	<u>4/05</u>
7.3	6.51	8.97	8.5	9.62	6.01	8.25
Testosterone.....						571

<u>4/05</u>	<u>6/05</u>	<u>10/05</u>	<u>1/06</u>	<u>5/06</u>	<u>10/06</u>	<u>1/07</u>
8.25	5.53	8.98	6.21	7.7	6.1	4.89

As of March 27, 2007, it has been over 13 ½ years since his only cycle of THB® was given; over 12 ½ years since HB was completed.

Fred's 1/07 PSA is his lowest since 6/03.

If this works so well, why isn't everyone using this?

Why am I the only one you are afraid to believe?

-Dr. Bob

Case Reports: Ottis R. – 1

Ottis R.

5/98: 68 years old; gl. 3+4/7; T_{1C}; PSA = 12.8

6/98: L + 1C + P

8/98: Consult with Dr. Bob; Advised to increase to 3C, but no \$ so took 6F
At times used some C stash from brother-in-law and some days took
1 or 2C; other days took 6F

7/99: Discontinued HB

7/00: PSA = 2.3; T = 182

10/00: PSA = 5.5

Case Reports: Ottis R. – 2

Ottis R.

3/02 → 3/04: PSA = 6-7; prior to 3/02 PSA < 5

3/04: PSA = 8.4; Start thalidomide

7/04: PSA = 6.32

6/06: PSA = 3.3

9/04: PSA = 4.64

7/06: PSA = 2.09

7/05: PSA = 4.0

1/07: PSA = 2.02

11/05: PSA 3.2

3/8/07: PSA = 1.8

1/06: Start Leukine and Revlimid
PSA = 3.62

After 3 years AAC, PSA = 8.4 to 1.8 (78% decline)

TRT Case Reports: Dr. Terry N. – 1

Dr. Terry N. - Veterinarian

- 2/99: 66 years old; PSA = 5.9
gl 3 + 4/7; PNI locally advanced; 4/5 cores; T = 350
- 5/99: F 250mg BID, P x 2 weeks then added L
- 6/28/99: Consult at COMG; PSA = 0.69; T < 20
F changed to 3 Casodex per day
THB® thru 6/00
- 1/03: PSA = 0.6; T = 332;
START TRT

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

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TRT Case Reports: Dr. Terry N. – 2

Dr. Terry N. - Veterinarian

	2/03	4/03	7/03	10/03	11/03	1/04
T	604	553	1749	1556	1085	1152
PSA	1.5	1.5	1.86	4.16	1.73	2.02

	3/04	6/04	8/04	9/04	11/04	1/05
T	1474	1544	1440	1189	1553	1830
PSA	2.13	2.62	3.34	2.01	3.41	1.78

	5/05	8/05	10/05	11/05	2/06	3/06
T	>1600	1064	1482	2665	3425	1510
PSA	2.44	3.14	4.53	3.49	4.48	6.02

	4/10/2006	4/19/06	5/10/06	5/31/06	6/06	7/06	3/07
T	2837	2665	3367	3401	3811	2153	5307
PSA	8.1	6.16	4.92	6.2	5.88	4.29	2.93

TRT Case Reports: Bob S. – 1

Bob S.

- 11/92: 72 years old; PSA 6.1; gl. 4+3/7; 6 out of 6 cores; 20-80%
Lt. iliac and obturator nodes; rib mets and L-3
- 11/30/92: Lupron + 6 Flutamide per day
- 1996: bone scan - normal
- 01/97: C-T scans - no nodes
- 03/97: Consult at COMG; had been on CAB for 4 years and 4 months;
PSA <0.05; T = 16
Discontinued hormone blockade
start Finasteride Maintenance[®] therapy
- 9/98: PSA = 0.04, T = 46; TRT until 2/99
- 9/02: Restart TRT

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

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TRT Case Reports: Bob S. – 2

Bob S.

	12/02	3/03	6/03	10/03	5/04	8/04
T	955	1476	>1600	1310	2001	2390
PSA	0.235	0.422	0.585	0.535	0.672	0.852

	10/04	2/05	6/1/05	8/05	9/21/05	9/05
T	1796	>1600	>1600	4128	3675	stop T
PSA	1.130	2.350	1.940	4.390	5.180	stop T

	9/28/05	10/05	11/05	12/05	3/06	7/06
T	260	127	118	64	42	<20
PSA	3.170	1.840	0.243	0.091	0.015	<.003

	8/06	3/07
T	<20	20
PSA	<.003	<0.003

- Not on HB
- Scans in 2005 – no metastasis

TRT Case Reports: Mark W. – 1

Mark W.

1/99: 52 years old

3/99: PSA = 11.61; T = 164

4/99: PSA = 17.54; T = 251; gl 4+5/9 at JHH, 50-90%; 3/6 cores
Prostascint - multiple enlarged periaortic and pericaval nodes (D1)
T_{1C}; THB[®] with 3 C/day

3/00: PSA < 0.05 (OTC's)

5/00: Discontinued THB[®]

1/02: PSA = 1.08; T = 152; Start TRT

12/03: Started on AAC

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

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TRT Case Reports: Mark W. – 2

Mark W. (cont.)

	8/02	10/02	12/02	2/03	6/03	8/03
T	437	941	1600	1600	641	764
PSA	2.45	3.8	5.86	6.64	8.88	9.76

	9/03	11/03	2/04	5/04	7/04	10/04
T	2627	1943	1306	1450	4163	1580
PSA	11.8	10.9	13.5	17.6	21.7	20.1

	12/04	1/05	2/05	3/05	4/05	D/C TRT
T	1474	632	312	1095	1270	D/C TRT
PSA	17.1	18.6	16.5	18	22	D/C TRT

TRT Case Reports: Mark W. – 3

Mark W. (cont.)

	5/05	8/05	10/05	12/05	3/06	4/06
T	90	158	162	173	230	133
PSA	11.9	4.14	4.1	4.91	3.56	5.24

	5/06	7/06	8/06	3/07
T	170	174	142	258
PSA	3.37	3.84	5.48	4.84

TRT Case Reports: Mark W. – 4

Mark W. (cont.)

- As of 3/27/07, 8 years after CaP diagnosis: gl. 9; PSA = 17.5; D₁
- Treatment with 1 cycle Triple Hormone Blockade[®]
- No local therapy; no chemotherapy
- 3 plus years of high dose TRT plus AAC
- Off T for 2 years and PSA stable since 8.05 and T higher than 3/99

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at <http://www.compassionateoncology.org/publications.html>)

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Intermittent chemotherapy: COMG Successful Approaches

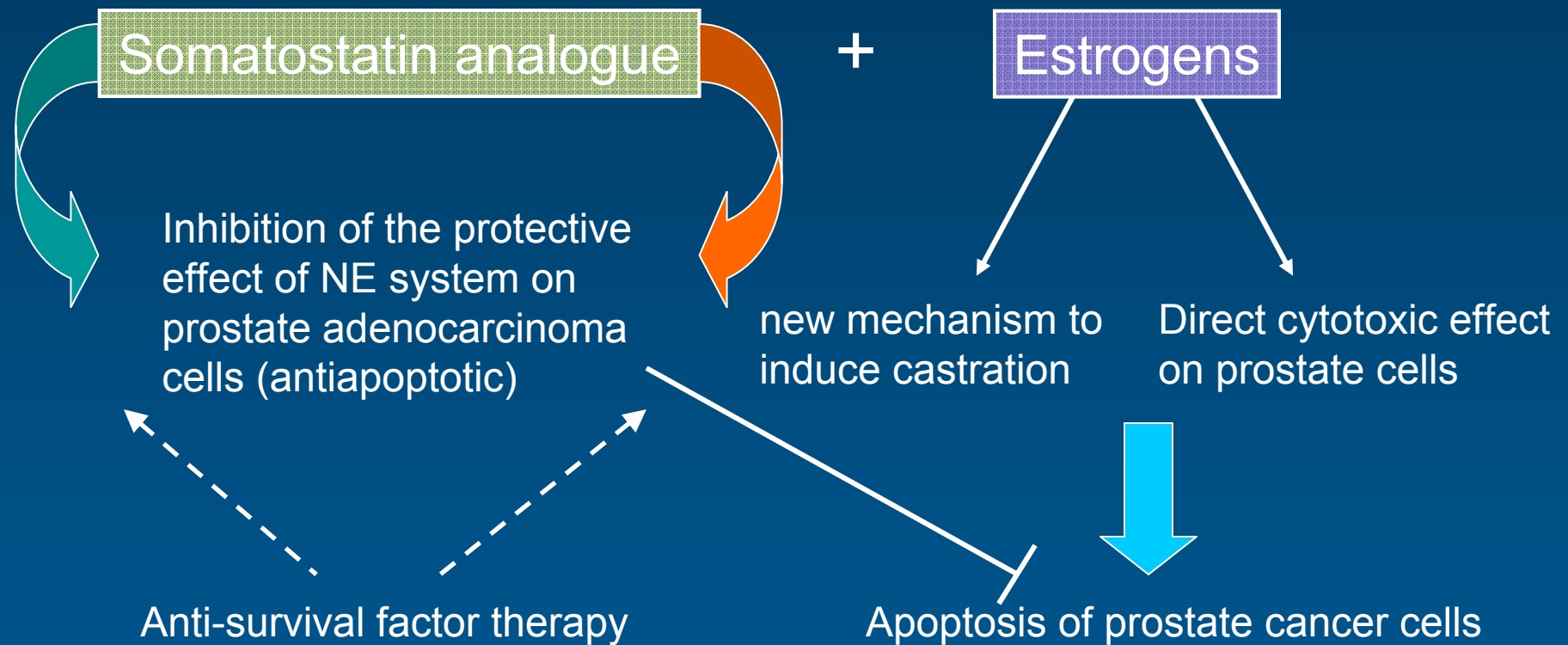
- Every month that a PT with met. CaP remains on HB, brings him 1 month closer to HRPC and thus shortens his life span
- Every month that a PT. with met. CaP survives with a normal to high testosterone level, is an extra month of excellent quality of life added to his life span
- You cannot develop HRPC unless someone puts you back on HB

Intermittent chemotherapy: COMG Successful Approaches

- In my opinion, your survival does not become threatened unless or until you develop a rising PSA while on HB (HRPC)
- If we can find ways to postpone or even better, prevent the need to go back on HB, then our treatment is prolonging your life span

Dr. Bob, circa 2001

"Rationale for our combination therapy with somatostatin analogue and estrogen"



HRPC: Sandostatin (STS) and Ethinyl Estradiol (EE) - 1

- Sandostatin analogues such as octreotide or lanreotide inhibit neuroendocrine (NE) cell tumors
- As single agents they were sometimes effective in Pts. with met. HRPC
- STS analogues inhibit the release of certain NE products such as IGF-1 And GH
- The best report was a PSA decline of $\geq 50\%$ in 20% of Pts. but 25-40% response in bone pain or performance status

HRPC: Sandostatin (STS) and Ethinyl Estradiol (EE) - 2

- As of January 2004, 20 Pts. with met. HRPC were treated with EE and Lanreotide
 - 19 of 20 Pts. (95%) had a $\geq 50\%$ PSA response
 - 2 of 20 Pts. died of met. CaP at 10 and 16 mos
 - 6 of 20 Pts. progressed
 - The other 14 (70%) are without progression at a median of 16.5 mos.

Taxotere Plus Ethinyl Estradiol

26 Pts. treated with 5mg DES plus

Taxotere 36 mg/m² 3 weeks on, 1 week off

- Average Age = 68 years old
- Average PSA = 67

Results:

- PSA decreased ≥ 90 for 39%
- 17 of 23 (74%) Pts. had PSA responses

COMG Protocol Validation

Phase II trial of Thalidomide, Avastin and Taxotere

Study:

- 33 Metastatic HRPC Pts.
- Taxotere, thalidomide, Avastin and LMWH
- Age = 67
- PSA = 87

Results:

- 28 Pts. (85%) had PSA decline \geq 50%
- 3 Pts. with 40% PSA decrease
- 2 Pts. with stable PSA

COMG Protocol Validation

Phase II trial of Thalidomide, Avastin and Taxotere

Conclusions:

- This is the first study to combine antiangiogenic agents of different mechanisms with Taxotere in metastatic HRPC
- This regimen has a high durable PSA decline rate (85%) with acceptable toxicities

CaP Chemohormonal Treatment: Sequential or Simultaneous - 1

- A very significant percentage of CaP investigators are using a sequential schedule of chemotherapy (CT) and hormone blockade (HB)
- In 1997, I concluded that concurrent CT/HB was most effective although in breast cancer, sequential is better
- A recent article studied responses in mice to address this issue

CaP Chemohormonal Treatment Sequential: or Simultaneous - 2

- Mice treated first with Taxol had a marked lack of response later to castration
- The authors concluded that simultaneous CT/HB is significantly more effective than either
- HB→CT or CT→HB
- The simultaneous group survived about 50% longer than either sequential group

TRT Case Reports: John S. – 1

John S.

01/03: 55 years old - A.A.; PSA 7.7; gl. 3+4/7; 6/6 cores;
Endorectal MRI - ECE

03/03: R.P. @ Memorial-Sloan Kettering, 2 pos. nodes, gl. 4+4/8;
SV. pos. margins; ECE; 2500cc EBL

07/03: PSA unmeasurable

04/04: PSA = 0.7

12/03: PSA = 0.23

06/14/04: PSA = 1.02

01/04: PSA = 0.35

08/4/04: PSA = 1.98; PSA DT = 2 mos.; T = 334; PAP = 0.15

Rx 13 mos THB[®] (KC/HC), plus 15 doses T/E/C; AAC added as tolerated

8/05: Discontinued HB; continue AAC and added high dose TRT

Data obtained from Dr. Bob's "TRT Case Reports" (available for free download at
<http://www.compassionateoncology.org/publications.html>)

® Triple hormone blockade, triple androgen blockade, and finasteride maintenance are the registered trademarks of Robert L. Leibowitz, M.D.

TRT Case Reports: John S. – 2

John S.

	9/05	10/05	11/05	12/05	1/06	2/06
T	4064	3961	4421	2620	2433	2406
PSA	<.01	<.01	<.01	<.01	<.01	<.01

	3/06	4/06	5/06	6/06	2/07
T	2901	2921	2815	1708	2691
PSA	<.01	<.01	<.01	<.01	<0.01

Case Reports: David S. – 1

David S.

02/95: 46 years old; T2A; PSA = 7; gl. 4 + 3/7 3/6 cores; L x 3 months

05/95: R.P. bilat. SV; ECE; bilat. 4+3/7

07/95: PSA < 0.5

7/00: PSA < 0.5

07/97: PSA = 0.7

08/01: PSA = 1.5; cycle #3 HB
L + 1C

8/97: PSA = 0.9

03/02: PSA = 16

11/97: PSA = 1.5 to 2.0; R.T.

06/02: nadir PSA 1.6

4/99: PSA nadir 0.6

11/02: PSA = 1.9; HRPC

7/99: PSA = 0.8; Start cycle #2 HB
L + 1C x 12 months

04/03: C stopped when PSA = 5.1

07/03: C-T pelvis – Lt. pelvic sidewall mass (nodes)

Case Reports: David S. – 2

David S.

- 12/03: PSA = 14.8; pelvic mass increased
- 03/04: Provenge (Dendreon product) started
- 04/04: Met. to Rt. femur
- 05/04: Increased Rt. femur met.
- 06/04: Increased Rt. femur met.
- 07/04: R.T. Rt. proximal femur
- 09/04: Increased size Lt. pelvic met.
- 10/04: R.T. Lt. pelvis
- 04/05: new mets. upper cx. spine and 2 in Rt. mid-femur and Lt. temple

Case Reports: David S. – 3

David S.

- 02/06: Increased pain in Rt. hip and femur; needed cane
MRI – met. C₆ engulfing C₆ nerve root
RUE numbness, weakness and neck pain
MRI – 4 or 5 mets. Rt. femur
- 3/06: PSA = 27 – had been on HB since 8/01
R.T. cx. spine and added 1C per day
- 4/18/06: Consult with Dr. Bob; PSA = 29.1; T < 20
T/E/C; alternate HB; AAC
- 6/06: PSA = 0.928; no bone pain
- 08/06: MRI cx. spine: mass gone; T/E/C completed; PSA = 0.16
- 11/06: PSA = 0.05
- 02/1/07: PSA = 0.02; Discontinue HB; continue AAC; Start TRT

Case Reports: David S. – 4

David S.

02/07/07: PSA = 0.17; T = 712
02/20/07: PSA = 0.5; T = 1248
02/28/07: PSA = 0.921; T = 1301
03/08/07: PSA = 0.75; T = 1579
03/14/07: PSA = 0.57; T = 3075

Case Reports: John L. – 1

John L.

- 9/97: PSA = 48; DRE – Stony hard Rt. and Lt.
gl. 4+3/7; 5/6 cores, although 1 was 3+5/8; bone scan – multiple mets.
- 4/98: PSA = 52; Start cycle #1 HB L + F
- 6/99: Consult with Dr. Bob; PSA = 0.07; T = 21
Discontinue HB; Start P
- 10/99 PSA = 4.29; T = 236
- 1/00: PSA = 12; T = 398; Start thalidomide
- 12/00: PSA = 11
- 08/01: PSA = 39; Start cycle #2 HB; A/G HC; T/E/C x 18 doses and AAC
- 01/02: PSA < 0.01
- 05/02: Discontinue HB

Case Reports: John L. – 2

John L. (cont.)

- 5/24/02: Discontinue HB; continue AAC; add TRT cycle #1
- 12/02: Discontinue TRT
- 2/03: Start HB cycle #3
- 6/03: Start TRT cycle #2 (thru 12/03)
- 12/03: Start HB cycle #4; PSA = 33 → 10 mos. PSA = 0.402
- 10/04: Start TRT cycle #3 x 3 months
- 01/05: PSA = 26.9; Start HB cycle #5; EE
- 2/28/05: Start chemotherapy cycle #2
- 04/05: PSA = 0.068

Case Reports: John L. – 3

John L. (cont.)

03/06: Start TRT #4
PSA = 0.008

04/06: PSA = 9.73; T = 1900

05/06: PSA = 18.4; T = 1250

06/20/06: PSA = 26.4; T = 2274

08/04/06: PSA = 36.9; T > 1500

08/22/06: PSA = 39.5; T = 1415

Start new med.

Case Reports: John L. – 4

John L. (cont.)

08/29/06: PSA = 25; T = 4569

08/07/06: PSA = 8.53; T = 849

10/04/06: PSA = 5.42; T = 1210

11/29/06: PSA = 4.22; T = 1365

01/23/07: PSA = 5.43; T = 1235

02/06/07: PSA = 4.8; T = 2867

March 14, 2007: PSA < 0.01; T = 973

Case Reports: Dave W. – 1

Dave W.

- 02/98: 54 years old; PSA = 681; locally advanced
gl. 4+4/8 6/6 at John Hopkins Hospital
Multiple bone metastasis
Enlarged nodes at chest, diaphragmatic, paracaval, iliac
Start cycle #1 HB - L + 3c
- 03/98: IP added
- 04/17/98: COMG: Taxotere/Emcyct/D x 16 doses → PSA = 0.2
- 03/99: Add thalidomide
- 05/99: Discontinue HB
- 12/99: PSA = 23; T = 263
- 01/00: PSA = 46
- 2/10/00: Start cycle #2 HB and start cycle #2 chemotherapy; PSA = 94
Taxotere/Emcyct/Carboplatin x 21 doses
- 03/00: PSA = 1.59; HB x 12 months
- 02/01: Discontinue HB

Case Reports: Dave W. – 2

Dave W. (cont.)

- 09/01: Start cycle #3 HB and chemotherapy; PSA = 70
Taxotere/Emcyt/Gemzar + Herceptin + Leukine; Adrenolytic
- 10/01: PSA = 1.6
- 12/01: PSA < 0.01
- 02/02: More AAC meds
- 05/02: Discontinue HB; TRT #1 x 4 months
- 09/02: Start cycle #4 HB; AAC; No chemotherapy; PSA = 56
- 01/03: PSA = 0.138; TRT #2
- 06/03: PSA = 130; PAP = 15; T = 602
Start cycle #5 HB x 9 months; cycle #4 chemotherapy
HDVD with Taxotere/Emcyt/Carboplatin x 15 doses

Case Reports: Dave W. – 3

Dave W. (cont.)

02/04: PSA = 0
04/04: Start cycle #3 TRT; TRT through 9/04
09/04: PSA = 83.7; PAP = 10; start cycle #6 HB; no chemotherapy
07/05: PSA = 0.05; start cycle #4 TRT x 3 months
10/05: Start cycle #7 HB + Avastin; no chemotherapy; PSA = 27
4 wks later: PSA = 1.8
01/06: PSA = 0.056
07/06: PSA = 0.011; discontinue HB

Case Reports: Dave W. – 4

Dave W. (cont.)

08/06: Cycle #5 TRT

01/07: PSA = 101.7; T = 1461; discontinued TRT; start cycle #8 HB

3 wks later: PSA = 8.9

03/15/07: Cycle #5 chemotherapy (off chemotherapy since 12/03)

03/23/07: PSA = 1.82 (10 weeks into HB treatment)

When first seen by COMG on 4/17/98, his PSA = 12.

Almost 9 years later, his PSA = 1.82 and he is NOT hormone resistant. He has worked full-time throughout and has never been hospitalized for CaP.

Advanced CaP

Chemotherapy

If high risk presentation 13 months THB[®] plus 12 doses weekly low dose Taxotere/Emcyt/Carboplatin (T/E/C) chemotherapy 3 weeks on, 1 week off.

If prior local treatment or HB, I usually use 15 doses T/E/C plus 9 months three drug HB but no anti-androgen if prior HB

If present with mets. or very high risk, 15 doses T/E/C and 13 months THB[®]

Advanced CaP

Prostate Cancer Anti-angiogenic Cocktail (PCAAC)

The worse the prognosis and the better the prescription coverage, the more I use AAC. These medications are used throughout treatment and are used for maintenance treatment for patients with higher risk disease. AAC is also used to help postpone or hopefully prevent the need to go back on HB

Testosterone Replacement Therapy - 1

- High Dose Testosterone Replacement Therapy (TRT) and CaP
- Target T level, 1800-3000mg
- In the lab, low levels of T stimulate CaP cells to grow, while high levels in a dose dependent fashion inhibit growth
- Bell shaped growth curve

Testosterone Replacement Therapy - 2

Agarwal, P et.al. Testosterone Replacement Therapy after primary treatment for prostate cancer. *Journal of Urology*. 2005; 173: 533-536.

Morgenthaler A et.al. Testosterone Replacement Therapy for men at risk for or with a history of prostate cancer. *Current Treatment Options in Oncology*. 2006; 7: 363-389.

Marks L et al. Effect of Testosterone Replacement Therapy on prostate tissue in men with late-onset hypogonadism. *JAMA*. 2006; 296(19): 2351-2361.

Testosterone Replacement Therapy - 3

- Triple Hormone Blockade[®]
- Compassionate Oncology Medical Group THB series of patients on finasteride maintenance[®] therapy have an average T level of just under 500
 - This level is approximately 25% higher than baseline since finasteride raises the level of T

Testosterone Replacement Therapy - 4

Therefore the critical question is not

Testosterone VS. No Testosterone;

But rather:

Is a T of 500 better or worse for CaP patients
compared to a T of 1800-3000mg?

Advanced CaP

High Dose Testosterone Replacement Therapy (TRT)

This subject should require an entire evening to do it justice.
Please refer to my website for 2 comprehensive papers on
TRT that I have written and updated

Download for free at www.compassionateoncology.org

Be happy,
Be well,
Live long and prosper.

-Dr. Bob

I would like to thank Joanna Tai, my office manager,
for making the slides and for all her assistance and support.

Promising New Therapies: Abiraterone - 1

Abiraterone (A) is an oral irreversible inhibitor of an adrenal enzyme necessary to make androgens, estrogen, and cortisone.

Despite hormone blockade, intratumoral T and DHT levels can be as high as levels found in men not on hormone blockade

Study:

18 Pts. – no dose limiting toxicity; 2 Pts. with high blood pressure

Promising New Therapies: Abiraterone - 2

Results:

- T levels became undetectable in all Pts.
- 70% had $\geq 50\%$ PSA decline
- 50% had $\geq 90\%$ PSA decline
- Regression of liver and bone metastasis seen
- 16 of 18 Pts. remain on treatment

Promising New Therapies: Abiraterone - 3

A separate study reports:

- 6 out of 6 Pts.: PSA decline
- 5 out of 6: PSA decline \geq 50%

Promising New Therapies: Satraplatin - 1

Satraplatin (S) is a novel oral platinum compound that has shown activity in a number of tumors including CaP

Study:

Double-blind prospectively randomized trial in metastatic HRPC Pts. who have progressed after 1 prior chemotherapy regimen:

S + prednisone vs. placebo + prednisone

- 80 mg/m² daily for 5 days every 5 weeks
- 950 Pts. entered over 28 months

Promising New Therapies: Satraplatin - 2

Results:

- Pts. on S had a 40% reduction in the risk of progression and the improvement increased over time
- Toxicities:
 - decreased WBC
 - Decreased platelets
 - GI was generally mild to moderate

Promising New Therapies: Satraplatin - 3

Conclusions:

S is a HIGHLY EFFECTIVE oral agent, with a favorable safety profile, which could be a valuable treatment option for patients with metastatic HRPC

Promising New Therapies: DMXAA (AS 1404)

DMXAA (AS 1404) is a small molecule agent that disrupts tumor vasculature

Phase II study metastatic HRPC

- Taxotere +/- DMXAA
- 64 Pts.
- PSA = 83

Results:

- Taxotere alone: 35% PSA response
29% Progressive disease
- Taxotere + DMXAA: 57% PSA response
17% Progressive disease

Promising Agents: GM-CSF, GVAX - 1

GVAX = A vaccine composed of whole CaP tumor cells including 2 allogeneic CaP cell lines that have been genetically modified to secrete GM-CSF

An initial study in Pts. with met. HRPC found a median survival of 26.2 mos., whereas the “predicted” survival was 19.5 mos.

Promising Agents: GM-CSF, GVAX - 2

Currently 2 GVAX studies are underway:

- GVAX vs. Taxotere and prednisone – met. HRPC without pain
- GVAX + Taxotere vs. Taxotere + prednisone – met. HRPC with pain

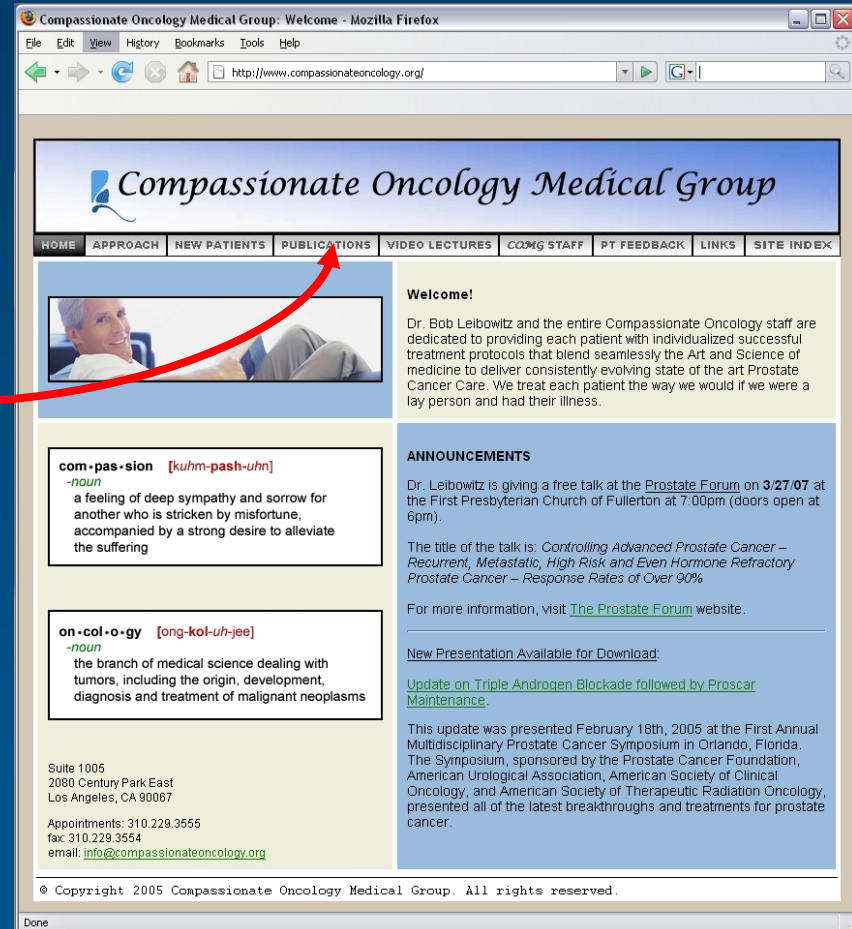
Protocol:

- GVAX 13 treatments every 2 weeks followed by monthly injection for life
- Taxotere every 3 weeks for 9 doses

Dr. Bob's website

<http://www.compassionateoncology.org>

Click on **Publications** in the toolbar to access the list of Dr. Bob's papers



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Compassionate Oncology Medical Group

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Welcome!

Dr. Bob Leibowitz and the entire Compassionate Oncology staff are dedicated to providing each patient with individualized successful treatment protocols that blend seamlessly the Art and Science of medicine to deliver consistently evolving state of the art Prostate Cancer Care. We treat each patient the way we would if we were a lay person and had their illness.

ANNOUNCEMENTS

Dr. Leibowitz is giving a free talk at the [Prostate Forum](#) on **3/27/07** at the First Presbyterian Church of Fullerton at 7:00pm (doors open at 6pm).

The title of the talk is: *Controlling Advanced Prostate Cancer – Recurrent, Metastatic, High Risk and Even Hormone Refractory Prostate Cancer – Response Rates of Over 90%*

For more information, visit [The Prostate Forum](#) website.

New Presentation Available for Download:

[Update on Triple Androgen Blockade followed by Proscar Maintenance.](#)

This update was presented February 18th, 2005 at the First Annual Multidisciplinary Prostate Cancer Symposium in Orlando, Florida. The Symposium, sponsored by the Prostate Cancer Foundation, American Urological Association, American Society of Clinical Oncology, and American Society of Therapeutic Radiation Oncology, presented all of the latest breakthroughs and treatments for prostate cancer.

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“In the first, it is ridiculed;
In the second, it is resisted;
In the third, it is considered
self-evident.”

-Schopenhauer, 1788-1860

“Is cure possible?

Is cure necessary?

Is cure possible only when
it is not necessary?”

-Dr. Whitmore

“There are more people making a living from prostate cancer than there are men dying from it.”

-Dr. Whitmore