Primary Triple Androgen Blockade (TAB) followed by Finasteride Maintenance (FM) for clinically localized prostate cancer (CL-PC): Long term follow-up and quality of life (QOL)

SJ Tucker, JN Roundy, RL Leibowitz; Compassionate Oncology Medical Group. 2005 Multidisciplinary Prostate Cancer Symposium, Orlando, FL. Abstract #106.

Background: Curative treatment strategies for CL-PC remain controversial and plagued with significant long-term declines in QOL. Recent reports describe frequent and increasing use of primary androgen deprivation (AD) in the setting of CL-PC. We report on our long-term results using a single 13 month cycle of TAB-FM as a management strategy for CL-PC.

Methods: We have prospectively treated 183 men with CL-PC who refused local therapy with TAB-FM. TAB consisted of 13 months of therapy with an LH-RH agonist and antiandrogen (bicalutamide or flutamide) plus finasteride 5 MG QD. All men were then given daily FM. QOL has been measured with a validated symptom-based scale for pen-based computers. Physical, psychological, and functional status, as well as global health-related QoL was recorded.

Results: Median age was 67, mean baseline PSA (bPSA) was 11.1 ng/mL (range 0.39–59.8) and median Gleason score (GS) of 7 (range 4–10). Mean baseline testosterone (T) was 398 ng/dL. High risk CL-PC (PSA > 20, or GS > 7, or T3 stage) was documented in 59/183 (32%) of men. At a median follow-up of 75 months (range 48-156; first 100 patients) mean PSA is 3.3 ng/mL. Mean current T is 487 ng/dl. A second cycle of AD has been initiated in 14/183 men; all 14 of these men have high risk CL-PC. One man developed metastatic PC and died from progressive resistant PC. No man with low or intermediate risk CL-PC has received a 2nd cycle of AD to date. Five men have proceeded with deferred local therapy 3-6 years after TAB. Disease specific survival is 99.4%. All patients experienced typical and expected toxicity of AD; all toxicities were reversible. Detailed QOL data will be presented in full.

Conclusions: A single 13 month cycle of TAB-FM provides excellent long-term control and management of CL-PC, including in men with high risk CL-PC. Evidence that any form of radical local therapy prolongs life is absent from prospective randomized trials. That such therapy has a serious and often permanent impact on potency, continence, or fecal function has been clearly proven. We suggest further exploration of TAB-FM as a safe and viable alternative to surgery, radiotherapy, or brachytherapy for CL-PC.

BACKGROUND

The treatment of “clinically” localized and PSA-detected prostate cancer (CL-PC) is remains controversial. Despite the absence of evidence that PSA screening is effective, some advocates argue for lower screening PSA thresholds while others recommend abandoning PSA screening completely. For men with CL-PC, typical curative treatment recommendations are various forms of surgery or radiation. Unfortunately no evidence exists from randomized clinical trials to support an overall survival benefit for these men compared to observation alone. Further, overwhelming evidence is available that any attempt at curative therapy will result in a high likelihood of long term complications such as impotence, urinary incontinence, and fecal bother. Even if a survival benefit does exist for early use of radical therapy as curative therapy, numerous validated nomograms are available to efficiently identify those men for whom PSA recurrence is more probable than possible, thus identifying men for who cure is not even likely. The majority of these men present with micrometastatic disease, undetectable by conventional imaging, and will ultimately require systemic therapy.

Early androgen deprivation (AD) is highly effective in advanced PC and provides a survival advantage for men with high risk PC or node positive PC treated with combined modality therapy. According to the CAPsure database, primary AD, while not often regarded as an option for CL-PC, has been significantly increasing in usage over the last decade, across all risk categories. For men with PSA recurrence and a rapid PSA doubling time, early AD is given as salvage therapy and may provide a survival advantage. Some authors have also identified that delayed AD is associated with an increased risk of a PC specific death. Last, intracellular AD, via 5-alpha reductase inhibition, has been shown to reduce the risk of healthy men developing PC by 24%, possibly by overall reduction in intracellular DHT levels.

For over 10 years we have eschewed radical therapies in favor of a single cycle of primary AD using Triple Androgen Blockade (TAB) followed by finasteride maintenance (FM). We use TAB-FM as a management strategy for CL-PC; given the high prevalence of CL-PC, we treat it as a chronic systemic disease, not an acute life-threatening illness. We present long-term follow-up, including quality of life (QOL), in a large cohort of men with CL-PC treated with TAB-FM as primary therapy.

MATERIALS AND METHODS

Patients:
We have been prospectively using a single cycle TAB-FM for greater than 10 years in men refusing radical local therapy. Demographics and outcomes have been tracked prospectively in an Excel database involving 217 men. All men had biopsy proven PC. Over 90% of patients had their pathology re-confirmed at an academic center. Initially, routine imaging was not performed to confirm CL-PC, but has been standard since 1999. Patients with clinical evidence of metastatic disease or histology other than adenocarcinoma are excluded from study. No patient had undergone any form of local therapy prior to TAB-FM. All patients were informed of the risks, benefits, and alternatives to hormone blockade before therapy was initiated.

Treatment:
TAB consists of an LHRH agonist (either leuprolide acetate [7.5 mg] or goserelin acetate [3.6 mg] every 28 days) plus an antiandrogen (either flutamide [750 mg] or bicalutamide [initially 50mg and later increased to 150 mg] daily) plus finasteride (5 mg daily) for a median of 13 months. Induction therapy was followed by maintenance therapy with finasteride (5 mg daily) for an indefinite period.

Outcome measurements:

- Long-term PSA and testosterone (T) levels
- Disease-specific survival
- Time to achieve unmeasurable PSA (defined as < 0.1 ng/ml)
- Re-treatment with any form of AD
- Development of androgen-independent PC (AIPC)
- Use of deferred local therapy

Measurements of PSA were made at 3-month intervals or less during treatment with TAB and at approximately 3-4 month intervals during FM. Blood samples were assayed for PSA at our clinic or by local community laboratories. Baseline and follow-up T levels were also measured at 3-month intervals until T levels reached baseline levels or a plateau. Testosterone was also measured during finasteride maintenance to assess androgen recovery. Complete blood counts and comprehensive chemistry panels including liver function tests were performed regularly while on TAB.

Quality of Life (QOL):
Prior to June 2001, at the majority of patient visits, clinical symptoms and adverse effects were recorded but not systematically logged in the TAB database. Since June of 2004 we have recorded QOL via hand held tablet based computers. The Cancer Care Monitor (CCM) is a symptom-based scale developed for administration on pen-based computers. The CCM provides ratings on 38 physical, psychological, and functional oriented items that comprise six symptom scales and one global QOL index. All additive scales are then converted to normalized T scores. CCM items can be scored as a reliable and valid measure of constructs related to physical, psychological, and functional status, and global health-related QOL in adult cancer patients (Journal of Pain and Symptom Management, Vol. 26 No. 6 December 2003).

RESULTS

Pre-treatment Characteristics (n=174)

	Mean	Median	Range
Age	66	67	46 - 86
PSA	11.9	8.2	0.4 - 59.8
Gleason	6.7	7	4 – 10
Testosterone	396	377	154 - 819

	PSA	< 10	10 – 20	> 20
Mean	11.9	6.1	13.8	28.5
Count	174	103	40	31

	Gleason	4 – 6	7	8 - 10
Median	7	6	7	8
Count	174	77	74	23

Stage	T1c	T2a	T2b	T2c	T3
Count	71	61	15	4	17

High Risk PC Characteristics:

	Mean	Median	Range
PSA	20.4	20.5	4.1 - 59.8
PSA > 20 (n=31)	28.5	-	-

Clinical stage T3: 17 men
Gleason Sum 8–10: 23 men
Gleason 4+3: 34 / 74 GS=7

57 / 174 patients with classic High Risk CL-PC
PSA Control with TAB-FM

Median time to achieve PSA < 0.1
4 months (range 1-10)

Median duration of TAB = 13 months (range 10-27)

Median follow-up = 60 months

Mean current PSA = 2.6 ng/ml Range (0.1 – 16.1)

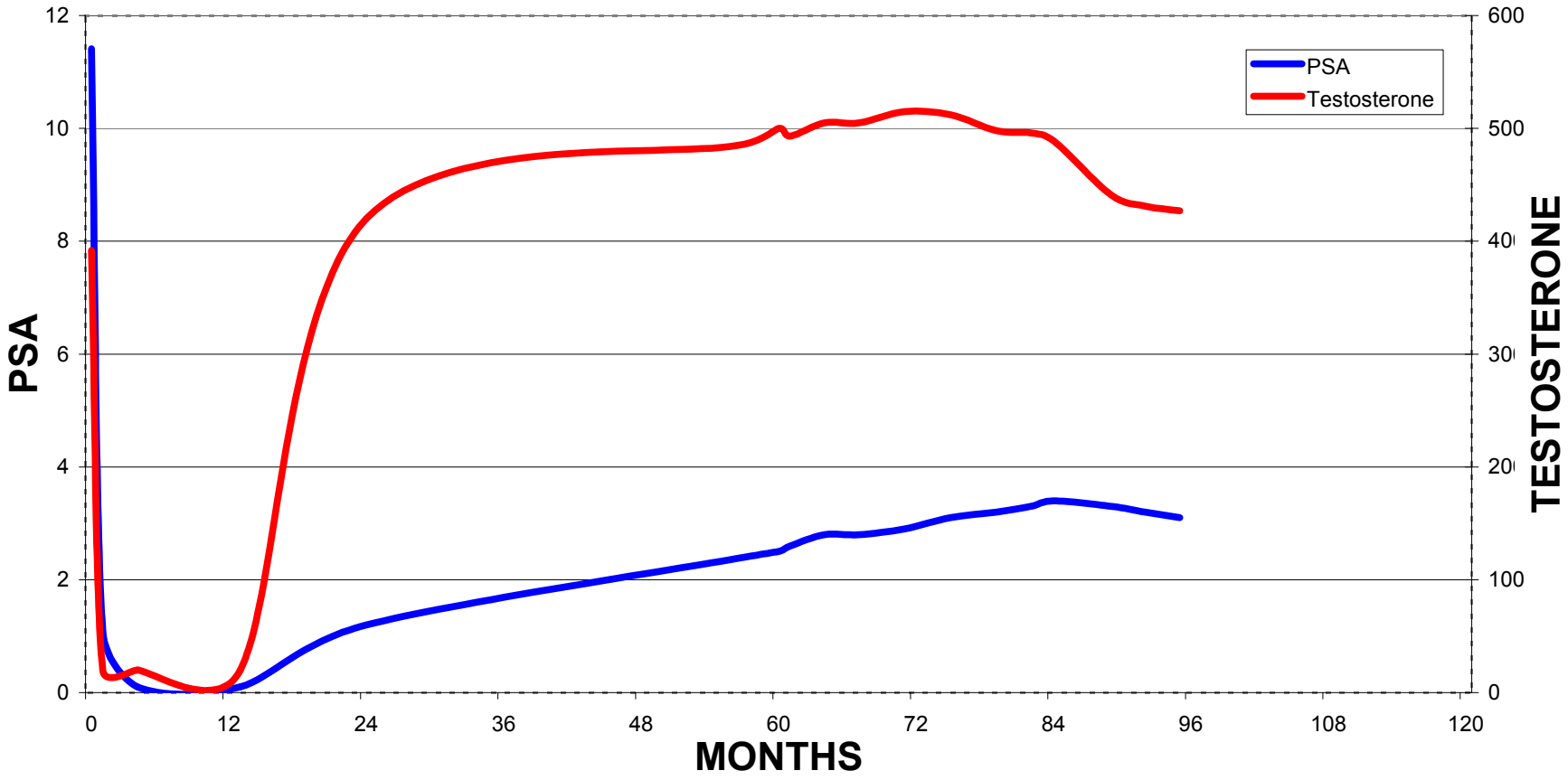
Mean current Testosterone = 493

Follow-up for the first 100 men in series:

Mean PSA:	**3.2 ng/ml (0.1 – 16.1)**
Median follow-up:	**78 months**
Minimum follow-up:	**51 months**
Longest follow-up:	**159 months**

Disease Specific survival is 99.4%.

TIME COURSE OF PSA AND TESTOSTERONE RECOVERY AFTER 13 MONTHS OF TRIPLE ANDROGEN BLOCKADE



Characteristics of Men in Cycle #2 Androgen Deprivation

Age	Stage	bPSA	GS	C#1 Start	C#1 End	Off ADT1	bPSA2	T2	C#2 Start	C#2 End	Off ADT2	f/u	Time Off	Notes
63	T3	13.94	7	Jun-00	Aug-01	35	13.1	433	Jun-04			53	66%	↓ Renal Cell
55	T1C	51.31	8	Feb-99	Mar-00	22	26.0	451	Jan-02			45	49%	Follow up lost
59	T1C	22.79	7	Apr-98	May-99	35	14.1	450	Apr-02	Jan-03	25	82	73%	
54	T3	4.5	8	Mar-97	Apr-98	32	6.9	893	Dec-00			51	63%	Brachytherapy
65	T1C	18	10	Oct-95	Dec-96	69	32.0	460	Sep-02	Jan-04	11	104	77%	
62	T2A	8.7	9	Apr-97	Jul-98	62	13.0	520	Sep-03	Apr-04	10	96	75%	
68	T2A	18.6	9	Jun-98	Jul-99	41	15.2	460	Dec-02	May-03	21	80	78%	
77	T3	43	9	Apr-98	Jun-99	26	14.7	465	Aug-01	Aug-02	16	82	51%	C#3
65	T2A	59.8	7	Mar-98	Apr-99	25	23.0	494	May-01	Mar-02	19	83	53%	C#3
72	T1C	13.5	8	Jun-97	Jul-98	64	18.8	267	Oct-03			92	70%	On ADT
69	T2C	19.2	8	May-98	Jun-99	27	25.0	581	Sep-01	May-02	n/a	49	55%	↓ CAD
69	T2A	3.97	8	Jun-98	Aug-99	43	11.9	450	Mar-03	May-04	9	80	65%	
66	T1C	14.4	7	May-99	Jul-00	43	8.2	810	Feb-04	Nov-04	3	69	67%	
73	T3	26	7	Aug-98	Sep-99	39	7.0	683	Dec-02	Nov-03	15	78	69%	
70	T1C	36.45	6	Mar-98	Apr-99	38	112.0	465	Jun-02	Mar-04	n/a	72	53%	↓ Met AIPC
57	T1C	23.71	6	Jul-99	Oct-00	31	15.1	917	May-03	Feb-04	15.1	67	47%	
60	T3	22	7	Mar-00	May-01	27	16.8	671	Aug-03	Jul-04	16.8	59	46%	
50	T3B	20.7	7	Sep-00	Jan-02	23	12.3	489	Jan-04	Jan-05	12.3	52	45%	
81	T3	10.0	7	Mar-97	May-98	77	13.8	421	Oct-04		13.8	95	81%	On C#2 ADT

Cycle #2 of AD initiated in 19 / 174 (11%) men
18 / 19 men presented with High Risk CL-PC

1 man developed AIPC with metastases
Succumbed to AIPC 6 years after diagnosis

39 / 57 men with High Risk PC have yet to require a 2nd cycle at a median follow-up of 5 years

Deferred Local Therapy (DLT) after Triple Androgen Blockade

Stage	bPSA	GS	TAB Start	TAB End	Date DLT	f/u to DLT	DLT
T3	4.5	8	3/97	4/98	3/01	48m	EBXRT + Seeds
T2B	7.32	7	6/98	8/99	1/04	67m	EBXRT + Seeds
T1C	6.3	7	1/98	2/99	10/03	69m	R.P.
T1C	6.7	7	1/98	4/99	12/03	71m	Proton Beam XRT
T2A	8.91	6	8/01	10/02	8/03	24m	Seeds
T2A	8.47	6	11/96	11/97	12/03	85m	Seeds

Quality of Life Data

QOL data available from 123/174 men

- 39 with follow-up < 24 months
- 87 with follow-up => 24 months

Since 07-30-2004: 259 CCM reports

Mean # visits: 2.1 (1-14)

QOL Median follow-up: 43 months

Severity Grade by Domain T-Scores

Item name	Value	Severity grade	Count	Percent
Treatment Side Effects				
	<=65	1	123	100.00
	> 65	2	0	0.0
Impaired Ambulation				
	<=65	1	102	82.93
	> 65	2	21	17.07
Despair/Depression				
	<=65	1	119	96.75
	> 65	2	4	3.25
Distress				
	<=65	1	117	95.12
	> 65	2	6	4.88
General Physical Symptoms				
	<=65	1	115	93.50
	> 65	2	8	6.50
Impaired Performance				
	<=65	1	105	85.37
	> 65	2	18	14.63
Quality of Life				
	<=45	1	17	13.82
	> 45	2	106	86.18

- Physical, psychological, and general symptom normalized T-Scores were assessed for all men and stratified by follow-up < or > 24 months.
- All men, regardless of follow-up, report favorable psychological and general function scores consistent with lack of impacting or enduring toxicity from TAB-FM.
- Review of specific physical symptoms scores reveal mild problems with fatigue (1.83) and sleep habits (1.45) as well as moderate complaints of decreased sexual interest (3.38)
- Men in the first 24 months report higher complaints of decreased sexual enjoyment/interest than man after 24 months (4.49 vs. 2.84)
- Mild complaints regarding fatigue, sweats (hot flashes), and difficulty sleeping are also more pronounced in the first 24 months compared to after

Mean Severity Scores: Physical symptoms

	0 – 24 months	> 24 months
Fatigue	2.54	1.5
Sweating	1.69	0.59
↓ sexual enjoyment	4.49	2.84
Difficulty w/ sleep	2.56	0.9

Compared with normative data from validation trials of the CCM, men treated with TAB-FM enjoy significantly greater physical functioning, general health, and freedom from worry than the average cancer patient.

Quality of Life Before & After TAB

Mean T-Score value for most recent visit: Men with 1 to 24 month follow-up

Item name	Mean	Std	Min	Max	N
General Physical Symptom	47.87	10.13	28.81	69.62	39
Distress (Acute Distress)	46.66	9.33	37.93	71.97	39
Despair/Depression	47.85	8.15	42.92	71.31	39
Treatment Side Effects	41.74	5.88	34.96	57.59	39
Impaired Ambulation	48.61	6.32	46.61	72.65	39
Impaired Performance	44.52	10.99	36.32	71.41	39
Quality of Life	56.66	9.34	29.06	73.54	39

Mean T-Score value for most recent visit: Men with > 24 month follow-up

Item name	Mean	Std	Min	Max	N
General Physical Symptom	43.28	9.61	28.81	65.13	80
Distress (Acute Distress)	44.05	8.20	37.93	65.95	82
Despair/Depression	46.81	5.95	42.92	62.96	81
Treatment Side Effects	40.96	6.67	34.96	59.53	79
Impaired Ambulation	52.13	10.49	46.61	76.85	82
Impaired Performance	46.81	11.96	36.32	71.41	82
Quality of Life	57.02	10.69	33.86	73.54	79

T-test for QOL T-Scores

Item name	Mean		P-value for T-test	Total N
	0-24 month	>24		
General Physical Symptom	47.87	43.28	0.0180	119
Distress (Acute Distress)	46.66	44.05	0.1196	121
Despair/Depression	47.85	46.81	0.4775	120
Treatment Side Effects	41.74	40.96	0.5356	118
Impaired Ambulation	48.61	52.13	0.0239	121
Impaired Performance	44.52	46.81	0.3151	121
Quality of Life	56.66	57.02	0.8613	118

DISCUSSION

Despite optimism and enthusiasm, there are currently no markers to reliable discriminate men with CL-PC for whom an intervention may be beneficial. For patients, and most physicians, in North America, observation alone is unpalatable. Given the enduring complications of impotence & incontinence and the high probability of PSA recurrence, increasing numbers of men will refuse local therapy.

We have demonstrated that a single 13 month cycle of TAB-FM is a reasonable management strategy for CL-PC. Use of TAB-FM does not preclude local therapy in the future. Long-term follow-up shows excellent PSA control and more importantly a disease specific survival rate of > 99%.

Toxicity of TAB-FM is predictable and reversible. QOL data, while still immature, confirms reversibility of toxicity. CCM questionnaires are being modified to greater reflect the specific issues associated with AD in general.

We are currently using TAB-FM in the setting of an IRB approved clinical trial to further obtain toxicity data and define the time course of QOL change. TAB-FM should be utilized and tested more broadly in the prostate cancer community.

The authors acknowledge and appreciate the participation of Barry Fortner, Ph.D., and Ling Zhu, M.S., Ph.D. for their assistance with management of CCM generated QOL data and statistics.