Intermittent androgen suppression in prostate cancer: an update of the Vancouver experience

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Introduction: *This report will review the long-term follow-up of a prospective Phase II evaluation of intermittent androgen suppression in the treatment of prostate cancer. Specifically, this analysis will address completed cycle characteristics, the concept of prolonged off-treatment cycles, the time to cancer progression, cancer-specific survival and the association between PSA and bone scan changes.*

Methods: *A total of 102 patients have been entered into this protocol. Treatment was initiated with combined androgen blockade and continued for 6 months or longer to reach a serum PSA nadir. Medication was then withheld until the serum PSA increased to predetermined trigger points based on initial parameters. Each cycle of treatment and no-treatment was repeated until the regulation of PSA became biochemically androgen independent.*

Results: *One hundred two patients have been commenced on IAS with an average follow-up time of 219 weeks (range: 14.5 to 588). Ninety-one patients have completed at least one therapeutic cycle with a total of 188 completed cycles available for analysis. The average time off therapy (percentage time off therapy) for cycles 1, 2, 3 and 4 was 13 months (53%), 11 months (51%), 10 months (47%) and 8 months (45%), respectively. A prolonged off-treatment time of greater than 72 weeks was observed in 33 (18%) of all completed cycles, and was most common in the men being treated for radiation failure stage C. Progression and survival data was calculated for the entire trial cohort (n=102). The average time to androgen independent progression in the 29 (28%) patients who progressed was 194 weeks. Death from prostate cancer occurred in 19 (18%) patients at an average of 258 weeks following treatment initiation. A review of bone scans revealed 22 events of newly detected lesions, all but 2 of which were preceded by a rise in serum PSA.*

Conclusions: *Longer duration follow-up of a single cohort continues to support IAS as a viable treatment option for men with prostate cancer. This approach affords an improved quality of life when the patient is off therapy, with reduced toxicity and costs. There is a trend toward extended times to progression and death compared to contemporary studies of continuous androgen suppression. Randomized, prospective protocols are currently underway to determine whether survival is affected in a beneficial or adverse way in men with locally recurrent or metastatic cancer.*

Key Words: prostate cancer, intermittent androgen suppression

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Remembrance

Ernie Ramsey was a mentor and a good friend. Despite our differences in years, I felt that I could

discuss just about anything with this marvelous, well-rounded individual. Ernie was a strong promoter of research, both clinical and basic and he brought Canadian urology to the attention of urologists around the world. Ernie Ramsey was a man of his word and he lived by the highest moral standards. The year of the Winnipeg CUA, I was his program chair. It was during the review of some dubious abstracts that he taught me a lifelong lesson about research integrity and how important it was to deal head-on with questionable practices. I had many good times with Ernie and my only regret is that his tenure as Professor in Vancouver was so short-lived. Ernie, I miss you and I dedicate this manuscript to your memory.

Larry Goldenberg

Introduction

The trend towards early hormone withdrawal therapy has resulted in an increased potential for side effects as men spend more and more time in an androgen depleted state. Early on, androgen withdrawal results in hot flushes, loss of libido, impotence and general fatigue. Long-term castration leads to bone demineralization, anemia, lipid disorders and muscle wasting. Most importantly, biological processes, such as the upregulation of previously androgen-repressed survival genes, result in the emergence of androgen-independent (A-I) growth. One way to potentially lessen the severity of these side effects is through intermittent androgen suppression (IAS).[1]

Conceptually, IAS is based on the hypothesis that malignant prostate cells would remain in a hormone dependent state longer than under continuous therapy. The idea of inducing repeated regressions of androgen-dependent malignancy arose from the observation that the involution of prostate tissue brought on by castration is an active process involving the rapid elimination of a large number of epithelial cells.[2,3] If the malignant stem cells which survive androgen suppression could be forced into their normal pathway of differentiation by being re-exposed to androgens they may retain their apoptotic potential when exposed to subsequent androgen withdrawal. The results of experiments on animal tumor models supported this hypothesis.[4-6] In a mouse model, the androgen dependent LNCaP tumor cell line demonstrated a three-fold increase in time to androgen independent growth with IAS compared to continuous suppression.[7] Similar results were found with the androgen dependent Shionogi mammary tumor in male mice where the time to androgen independent growth with continual androgen suppression of 50 days was extended to 150 days with up to five cycles of intermittent androgen suppression.[8]

Our centre, and others, have previously shown IAS to be clinically feasible[1,9,10] and studies have confirmed the improvement in patient well-being during the off-cycle of IAS.[11,12]

This report will review the long-term follow-up of a prospective Phase II evaluation of intermittent androgen suppression in the treatment of prostate cancer. Specifically, this analysis will address completed cycle characteristics, the concept of prolonged off-treatment cycles, the time to cancer progression, cancer-specific survival and the association between PSA and bone scan changes.

Subjects and methods

A total of 102 hormone-naïve patients with prostate cancer of a variety of grades and stages have been commenced on a previously described IAS protocol.[1] Therapy was commenced after full evaluation of the patient including bone scan and relevant x-rays for those thought to be at significant risk of metastatic disease.

Treatment

Treatment was initiated with combined androgen blockade. A treatment cycle is defined as the time between the initiation of medical castration to the time point of the start of the next treatment phase. Eligibility for the study was based on the attainment of a stable or decreasing serum PSA nadir in the normal range (≤ 4.0 ng/ml) between 24 and 32 weeks of the first cycle of androgen suppression. In several cases, particularly in the early part of the trial, first cycle treatment was extended to longer intervals exceeding 40 weeks.

When off therapy, 3 monthly follow-up continued to assess testosterone recovery and monitor for PSA rise. Treatment was recommenced when the serum PSA increased to an arbitrarily chosen value, as follows: Patients who had a pre-treatment serum PSA of greater than 20 ng/ml were started on their next cycle of therapy when the serum PSA increased to between 10 and 20 ng/ml. In men with an initial serum PSA between 10 and 20 ng/ml, treatment was resumed when the serum PSA level increased to between 5 and 15 ng/ml. Post radical prostatectomy patients resumed treatment when their PSA reached a level of 4 to 6 ng/ml.

TABLE 1. **Distribution of patients treated by intermittent androgen suppression according to clinical stage at entry**

Clinical stage	Number of patients
A2	3
B2	8
C-untreated	19
Radiation failure	22
Radical prostatectomy failure	16
D1	11
D2	23

Cycles of treatment and no-treatment were repeated until the regulation of PSA became biochemically androgen independent, that is, when the serum PSA did not fall into the normal range despite castrate levels of serum testosterone or when it increased after reaching a nadir despite serum testosterone being in the castrate range. In either situation, three successive increases in serum PSA above 4.0 ng/ml in the presence of suppressed levels of testosterone, was used to define progression to an androgen-independent state. Time to androgen independence was defined as the time point of the first of these three PSA increases.

Results

A total of 102 men have been commenced on our IAS protocol. The average age at entry into the study was 68.5 years (range: 41 to 92 years). The mean follow-up is 219 weeks (14.5 – 588) Table 1. The pre-treatment serum PSA values ranged from 0.2 to 4600 ng/ml with a median of 18.5 ng/ml and an average of 86 ng/ml. The average serum testosterone prior to treatment was 14.3 nmol/L (range: 7 to 25 nmol/L).

Number of cycles completed

At the time of this review a total of 91 men had completed at least one cycle of intermittent androgen suppression while 11 remained in the first off-treatment phase and are not included in the summary of cycle characteristics Table 2. There was a steady reduction in numbers of men who had completed subsequent cycles primarily due to insufficient follow-up. Almost all of the patients reached a PSA nadir of less than 2 ng/ml with each cycle. The time to reach PSA nadir ranged between 20 to 30 weeks. In general, the length of the cycles decreased with subsequent treatments although the portion of the cycle spent off therapy remained approximately 50%.

Time off treatment

The average time off treatment for the 188 cycles that have been completed to date is 47.5 weeks. There have been 33 (18%) cycles recorded where the time spent off therapy has exceeded 72 weeks. These occurred primarily in patients with moderately-well differentiated tumors and stage C disease, particularly those who have biochemically failed radiation therapy. Not surprisingly only a small portion of those patients with D2 disease had extensive off treatment periods Table 3.

Progression and cancer specific mortality

To date, 29 of the 102 patients have progressed to a state of androgen independence Table 4. The mean time to progression (TTP) was 194 weeks (median = 188 weeks). The median TTP of 188 weeks separated the 'early' progressors (at an average of 107 weeks), from the 'late" progressors (at an average of 266 weeks). The major difference in the characteristics of these two groups was their average pre-treatment PSA (396 ng/ml versus 40 ng/ml).

Not surprisingly, the majority of the AI progressors (19 of 29) had advanced stage D1 or D2 disease at the time of enrolment into the study. In 16 patients with

TABLE 2. **Overall cycle characteristics in 91 patients who have completed at least one cycle of intermittent androgen suppression**

Completed cycle #	1	2	3	4	5	6
# of patients	91	53	23	12	5	4
mean PSA at start (ng/ml)	94	19	15	18	17	15
mean time to PSA nadir (wks)	28	29	30	33	21	25
PSA nadir ≤ 2 ng/ml (% of pts)	95	94	96	100	80	100
mean length of cycle (wks)	95	86	84	72	63	67
mean time off therapy (wks)	50	44	40	32	30	35
mean time off therapy (%)	53	51	47	45	48	52

TABLE 3. **Cycle characteristics of patients with extended off-treatment periods (>72 weeks)**

Tumor grade	Number (%)	Tumor stage	Number (%)	% of stage
Well differentiated	4 (12)	A	1 (3)	33
Mod-well differentiated	21 (64)	B	2 (6)	25
Poorly differentiated	8 (24)	C – untreated	6 (18)	32
		C – post RRP	4 (12)	25
		C – post XRT	14 (43)	64
		D1	3 (9)	27
		D2	3 (9)	13
Total	**33**		**33**	

stage D2 on entry, A-I disease has occurred at a mean of 196 weeks.

Nineteen of 102 patients have died from prostate cancer: eleven stage D2, one stage D1, five stage C – post XRT, one stage C- untreated, and one stage C – post RRP. There have been three other non-prostate cancer related deaths. The overall mean time to death was 258 weeks, and for those with D2 disease, 231 weeks.

Correlation of PSA with bone scans in patients with D2 disease

All patients with skeletal metastases were reviewed to correlate PSA changes with bone scan findings. In 15 stage D2 patients who had sufficient numbers of follow-up bone scans to be evaluated, there were 22 events where new lesions were found on a bone scan. In all but two of these a PSA rise predated the development of these lesions. In the other two events the PSA rise began 2 and 6 months after the noted bone scan changes.

Discussion

Continuous androgen suppression as described by Huggins and Hodges in the treatment of advanced prostate cancer usually results in a positive response, the pattern of which is highly predictable.[13,14] Unfortunately, there are limitations to the continuous use of androgen withdrawal therapy. Treatment results in hot flushes, loss of libido, impotence and general fatigue, bone demineralization, anemia, lipid disorders, and muscle wasting.[15,16] Most importantly, for reasons that remain unknown, the cell death process induced by androgen ablation (by whatever means) fails to eliminate the entire malignant cell population and after a variable period of time,

TABLE 4. **Characteristics of patients with androgen independent disease progression**

	AI progressors n = 29	Early progression n = 15	Late progression n = 15
Average time to progression (wks)	194	107	266
Average PSA ng/ml	224	396	40
Clinical Stage			
B	1/8	0	1
C – untreated	2/22	1	1
C – post RRP	1/16	1	0
C – post XRT	6/22	3	3
D1	3/11	0	3
D2	16/23	9	7
Total	29/102	15	14
Tumor grade			
Well differentiated		0	1
Mod-well Differentiated		8	6
Poorly differentiated		6	7

averaging 24 months, the tumor inevitably recurs and is characterized by androgen-independent growth.[2]

Intermittent therapy with reversible androgen withdrawal therapies offers the potential for long-term control of prostate cancer while minimizing both short and long term side effects. The idea of inducing more than one regression of androgen-dependent malignancy arose from the observation that the involution of prostate tissue brought on by castration is an active process involving the rapid elimination of large number of epithelial cells.[17,18] It is postulated that the replacement of androgens, even in small amounts, would have a conditioning effect on surviving cells allowing them to conserve or regain desirable traits of differentiation.[18] The underlying assumption was that the maintenance of apoptotic potential by successive rounds of androgen withdrawal and replacement (intermittent androgen suppression) might forestall tumor progression. The availability of several luteinizing hormone-releasing hormone (LHRH) superagonists and of antiandrogens, and the potential for a full recovery from their action, made it possible to deliver ablative therapy in intermittent pulses.

In this report, we update the cohort previously described by the authors.[1] All patients tolerated the therapy well and responded in a positive physical and psychological manner to the cycling approach. They demonstrate the high response rate of prostate cancer to androgen suppression and the rapid decline of PSA to nadir levels. The results also demonstrate the potential for the cycling of hormone suppression and repletion to be repeated multiple times. Four of our patients have so far completed six or more cycles. The average 'off' treatment period for men on IAS was approximately 50% of the overall cycle, which enables men to regain physiologic androgen levels and hopefully reduces the likelihood of developing long-term side effects related to prolonged hormone withdrawal. There are a small number of cycles (18%) where the time without androgen suppression is impressively long (72 weeks), which would likely further improve the quality of life of those men. Prolonged times off treatment are most likely in men with lower stage and moderate grade disease.

These results, for the first time to our knowledge, report on A-I progression and mortality in a cohort of men with prostate cancer treated with intermittent androgen suppression. With a mean follow-up of 219 weeks, 29 (28%) of the patients have developed hormone refractory disease, and 19 (18%) have died of prostate cancer. The average time to progression was 194 weeks (48 months) and to death was 258 weeks (64 months). These times to progression and overall survival data are comparable to historical controls of continuous androgen withdrawal (and perhaps even better). However androgen withdrawal as a single modality and by any mode of delivery, is unlikely to cure this disease.

It may be argued that the high number of men in this cohort with early stage disease might bias toward these findings, but if only men with D1 and D2 disease are considered, the time to progression is still 196 weeks (48.5 months). These findings would need to be confirmed in an appropriately designed trial comparing IAS with continuous androgen withdrawal, but if the difference is found to be this large, it would have a major positive impact on the hormonal management of prostate cancer patients.

Despite the increasing numbers of patients enrolled in Phase II studies, available clinical information about intermittent androgen blockade is still limited. For example, it has not yet been confirmed in randomized clinical trials[19] whether it alters survival in a beneficial or adverse way. This approach affords an improved quality of life when the patient is off therapy as well as reduced toxicity and costs. At the present time it is not clear whether there are any patient characteristics, pathologic features or PSA-related response criteria that can be used to predict the length or number of cycles possible. As more patients are entered into prospective trials of intermittent androgen suppression, this information should become available.[19]

Conceivably, the intermittent therapy option will become an alternative to radical prostatectomy or irradiation for the primary treatment of localized prostate in older men with a life expectancy of less than 10 years. Augmentation of intermittent therapy to increase the length and number of cycles might be accomplished by the administration of cytotoxic drugs, differentiation agents or gene therapies at specific times during a cycle of treatment when the modality-of-choice would have its maximum effect. □

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