A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer

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OBJECTIVE

To compare the efficacy of lycopene plus orchidectomy with orchidectomy alone in the management of advanced prostate cancer.

PATIENTS AND METHODS

Fifty-four patients with histologically confirmed metastatic prostatic cancer (M1b or D2) and a performance status of 0–2 (World Health Organization) were entered into the trial between March 2000 and June 2002. The trial comprised two treatment arms, i.e. patients were randomized to orchidectomy alone or orchidectomy plus lycopene (OL), each of 27 patients. Lycopene was started on the day of orchidectomy at 2 mg twice daily. Patients were evaluated clinically before and every 3 months after the intervention, with measurements of prostate-specific antigen (PSA), a bone scan and uroflowmetry, with the clinical response assessed as the change in these variables.

RESULTS

At 6 months there was a significant reduction in PSA level in both treatments, but more marked in the OL group (mean 9.1 and 26.4 ng/mL, $P = 0.9$). After 2 years these changes were more consistent in the OL group (mean 3.01 and 9.02 ng/mL; $P < 0.001$). Eleven (40%) patients in orchidectomy and 21 (78%) in the OL group had a complete PSA response ($P < 0.05$), with a partial response in nine (33%) and four (15%), and progression in seven (25%) and two (7%), respectively ($P < 0.05$). Bone scans showed that in the orchidectomy arm only four (15%) patients had a complete response, vs eight (30%) in the OL group ($P < 0.02$), with a partial response in 19 (70%) and 17 (63%), and progression in four (15%) and two (7%), respectively ($P < 0.02$). There was a significant improvement in peak flow rate in the OL group, with a mean difference of +1.17 mL/s ($P < 0.04$). Of the 54 patients who entered the trial, 19 (35%) died, 12 (22%) in orchidectomy and seven (13%) in OL group ($P < 0.001$).

CONCLUSION

Adding lycopene to orchidectomy produced a more reliable and consistent decrease in serum PSA level; it not only shrinks the primary tumour but also diminishes the secondary tumours, providing better relief from bone pain and lower urinary tract symptoms, and improving survival compared with orchidectomy alone.

KEYWORDS

lycopene, prostate cancer, metastases, orchidectomy

INTRODUCTION

The remarkable association between a diet rich in fruits and vegetables and the reduced risk of several malignancies has lead to a consideration of the role of carotenoids in cancer prevention. Lycopene is one of the carotenoids that has emerged as important in the chemoprevention and treatment of various kinds of cancers, because of its unique properties of cancer prevention and regression, besides being a potent quencher of free radicals and an immunomodulator [1–3]. There have been few interventional trials in humans investigating the potential effect of lycopene supplementation for preventing and treating prostate cancer. We thus conducted a trial to compare the efficacy of lycopene plus orchidectomy with orchidectomy alone in the management of advanced prostate cancer.

PATIENTS AND METHODS

Fifty-four patients with histologically confirmed metastatic prostatic cancer (M1b or D2) and a WHO performance status of 0–2 [4] were entered into a trial between March 2000 and June 2002. The trial comprised two treatment arms, with patients randomized to orchidectomy alone or orchidectomy plus lycopene (OL), each of 27 patients. Patients treated with other methods, e.g. radiotherapy, chemotherapy or previous hormonal therapy, and with a life-expectancy of <3 months, were excluded from the study. Bone metastasis was diagnosed by bone scan and/or X-ray. Lycopene was started on the day of orchidectomy at 2 mg twice daily. Concurrent therapy included analgesics, antibiotics and occasionally surgery in patients with severe obstructive features. The patients were clinically evaluated before and every 3 months after orchidectomy, by serum PSA, a bone scan and uroflowmetry. Efficacy was evaluated primarily as the changes in PSA, the findings on bone scan and uroflowmetry. A complete response (CR) was defined as the serum PSA returning to normal (< 4 ng/mL) and/or a normal bone scan, and a partial response as a decrease in PSA level by more than half the initial value or as a reduction in metastatic mass by more than half of the initial level. Progressive disease was defined as any increase over the initial PSA by 25% or the development of any new 'hot spot' on bone scans. The best clinical response to treatment was assessed as changes in serum PSA level, bone scan and peak flow rate at ≥6 months. The changes in serum PSA levels were assessed at 6 months initially then at 2 years, while the other variables were

assessed at 2 years. All the patients were reviewed for a minimum follow-up of 2 years (24–28 months). The results were analysed statistically using the Wilcoxon signed-rank test, with overall survival calculated using the Kaplan-Meier method, with $P < 0.05$ considered to indicate statistical significance.

RESULTS

The distribution of patients and disease characteristics were well balanced in the two groups; Table 1 shows the patient characteristics at the time of entry in to the study. Baseline PSA levels were comparable in two treatment groups (Table 1). At 6 months there were significant reductions in PSA level in both arms, but it was more marked in the OL treatment, although not statistically significantly ($P = 0.9$). After 2 years the changes were more consistent in the OL group (Table 1) and were statistically significant ($P < 0.001$).

Based on the response criteria adopted, 11 patients in the orchidectomy and 21 in the OL group had a CR ($P < 0.05$) (Table 1); the progression rates were significantly different ($P < 0.05$). The follow-up bone scans (Table 1) showed that in the orchidectomy arm only four patients had a CR, compared with eight in the OL arm ($P < 0.02$); again the progression rates were significantly better in the OL group ($P < 0.02$). There was a linear relationship between the response based on the bone scan and the requirement for analgesics. Patients with a CR in both groups required no analgesics, but this was more evident in the OL group (25% vs 15%).

The baseline peak urinary flow rate was comparable between the groups (Table 1) but differed after intervention. There was a significant improvement in peak flow rate in the OL group ($P < 0.04$); there was also a significant subjective improvement in other voiding symptoms (frequency, urgency and dysuria, 80% vs 50%) in the two groups.

The mean (range) follow-up of the patients still alive was 25.5 (24–28) months; Fig. 1 shows the duration of survival in two groups. Of the 54 patients who entered the trial, 19 (35%) died, 12 (22%) in the orchidectomy and seven (13%) in the OL groups ($P < 0.001$). The causes of death were malignancy in 17 (31%) and cardiovascular in two (4%) patients (one in each arm). All the patients in the OL arm tolerated the drug well and there were no adverse reactions.

TABLE 1 Patient characteristics at the time of entry, PSA changes, and the clinical response to treatment based on PSA changes and bone scans

Characteristic	Orchidectomy	OL
N (%):		
Age group, years		
< 60	10 (37)	9 (33)
> 60–75	10 (37)	11 (41)
> 75	7 (26)	7 (26)
WHO performance status		
0	9 (33)	10 (37)
1	11 (41)	11 (47)
2	7 (26)	6 (22)
Metastatic pain at entry		
None	3 (11)	2 (7)
Mild	7 (26)	7 (26)
Moderate	6 (22)	7 (26)
Severe	3 (11)	3 (11)
Intractable	8 (30)	8 (30)
Voiding symptoms		
None	2 (7)	2 (7)
Minimal	8 (30)	9 (33)
Moderate	7 (26)	7 (26)
Severe	10 (37)	9 (33)
PSA changes at 6 and 24 months		
Mean (SD, range), ng/mL		
Initial	259.7 (860.5, 12–4500)	250.7 (857.3, 15–4300)
6 months	26.4 (66.3, 0.90–300)	9.1 (29.7, 0.7–150)
24 months	9.0 (7.5, 1.3–25)	3.0 (1.9, 0.7–13)†
Clinical response, n (%)		
PSA		
Complete	11 (40)	21 (78)*
Partial	9 (33)	4 (15)
Progression	7 (25)	2 (7)*
Bone scan		
Complete	4 (15)	8 (25)*
Partial	19 (70)	17 (63)
Progression	4 (15)	2 (7)*
Peak flow rate		
Mean (SD, range), mL/s		
Baseline	10.5 (1.29, 8.9–12.5)	10.24 (1.55, 8–12.5)*
After intervention	11. 0 (2.6, 2. 50–13.9)	12.2 (2.7, 6.5–15. 90)

*$P < 0.05$; †$P < 0.001$.

DISCUSSION

About a third of patients diagnosed with prostate cancer will present with advanced disease. Androgen ablation by castration, antiandrogens or LHRH analogues remain the standard of care for these patients. However, responses are transient in most patients, with progression to hormone-refractory disease being inevitable over 2–3 years. Advances in molecular and cellular biology have led to an improved understanding of prostate biology and the characteristics of prostate cancer. Based on this improved understanding, several new approaches are being developed for treating metastatic prostate cancer. These range from traditional dietary modifications to altering the microcellular environment

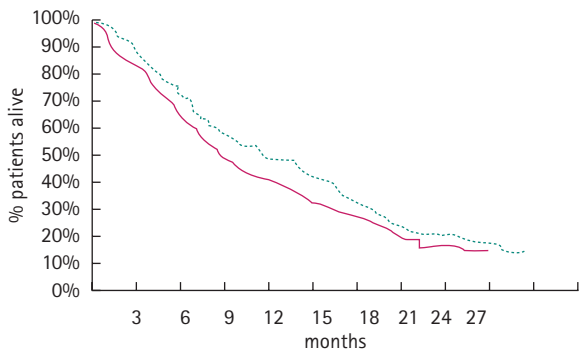

FIG. 1.
The Kaplan-Meier curve for the duration of survival in the OL group (red line) and control (green dashed line).

of the prostate cancer cell, and gene therapy.

Among the many carotenoids lycopene has been of special interest and has recently received attention because of suggestive associations in reducing the risk of cancer at many sites, including breast, prostate and pancreas. Lycopene is one of the major carotenoids in the diet and accounts for about half the carotenoids in human serum. The anticancer action of this carotenoid can be explained by several mechanisms; (i) inhibition of cell proliferation [2]; (ii) induction of cell differentiation and apoptosis; (iii) antioxidant, singlet-oxygen quencher and protection against oxidative DNA damage [3–7]; (iv) potentiation of the immune system; and (v) stimulation of gap junction communication [8]. Through these mechanisms lycopene controls cell proliferation and facilitates tumour regression.

Epidemiological data suggest that the environment is responsible for most prostate cancers. One major mechanism by which the environment can influence carcinogenesis is oxidative damage, i.e. the generation of reactive oxygen species that act as free radicals and damage important biomolecules, including DNA, proteins and lipids. An antioxidant is defined as any compound which breaks the free-radical reaction chain. Tomatoes are the primary dietary source of lycopene, which is one of the most potent antioxidants among the carotenoids [9–12]. Many experimental studies also support the view that oxidative damage is associated with prostate cancer. There is an association between prostate cancer and dietary fat consumption (a major substrate for oxidative stress), and oxidative biomarker data suggest increased oxidative stress among patients with prostate cancer. There are ubiquitous defects in the glutathione-s-transferase-π pathway (a major endogenous antioxidant mechanism), and evidence that androgens (an important promoter of prostate cancer growth) work in part by generating reactive oxygen species.

In a recent study, Chen *et al.* [13] examined the effects of lycopene on oxidative DNA damage and PSA levels in patients with localized prostate cancer. Thirty-two patients consumed tomato sauce-based pasta dishes for the 3 weeks (30 mg of lycopene per day) before their scheduled radical prostatectomy. Serum PSA levels decreased after the intervention, from 10.9 to 8.7 ng/mL, i.e. by 17.5% ($P < 0.001$). In a similar study, Kucuk *et al.* [14] obtained a PSA decrease of 18% after administering 15 mg of lycopene twice daily for 3 weeks, whereas it increased by 14% in the control group ($P = 0.25$). In the present study the decrease in PSA level was also greater in the OL group (Table 1) at 6 months. These changes were more consistent at 2 years ($P < 0.01$). The reasons for this consistent and more durable decrease in PSA level in the OL group can be attributed to lycopene-induced protective mechanisms, e.g. possible escape from the usual hormone-independent state at 1.5–3 years, antiproliferative activity, normalization of cell differentiation and regulation of apoptosis.

Besides being an antioxidant and singlet oxygen quencher, lycopene also inhibits cell proliferation, and induces cell differentiation and apoptosis [2]. Pastori *et al.* [15] reported that simultaneous addition of lycopene and α-tocopherol, at physiological concentrations (< 1 and 50 μmol/L, respectively) resulted in strong inhibition of prostate cancer cell proliferation of up to 90%. Kotake-Nara *et al.* [1] assessed the effects of 15 kinds of carotenoids on the viability of three lines of human prostate cancer cells, PC-3, DU 145 and LNCaP. Acyclic carotenoids such as phytofluene, zeta-carotene and lycopene, all of which are present in tomato, significantly inhibited cell proliferation and reduced cell viability. Logically this antiproliferative and inhibitory effect should act on the primary malignancy and metastasis, helping to reduce the gland and the secondaries. Kucuk *et al.* [14] conducted a randomized trial of 26 men with newly diagnosed, clinically localized (14 T1 and 12 T2) prostate cancer (15 mg of lycopene twice daily, 15 men, or no supplementation, 11 men) for 3 weeks before radical prostatectomy. Eleven men in the lycopene group and two in the control group had no involvement of surgical margins and/or extraprostatic tissues by cancer ($P = 0.02$). Twelve men in the lycopene and five in the control group had tumours of < 4 mL ($P = 0.22$). This suggests that the process of malignant transformation declined and the tumour regressed. The present data also show similar beneficial changes on bone scans, with twice the rate of CR (regression of bone secondaries) in the OL than in the control group. Similarly, there was greater disease progression in the control group at 6 months, and a greater improvement in peak flow rate and other voiding symptoms secondary to the reduction of the malignant gland, further supporting the anticancer properties of lycopene. Lycopene has also shown a dramatic response in hormone-resistant prostate cancer, opening a new possible treatment for such difficult patients [16].

There was a longer overall survival in the OL group ($P < 0.01$) than after orchidectomy alone, but it is too early to be sure that the survival benefit would be statistically significant in the long-term. Appropriate long-term randomized studies are required to provide further evidence to these observations.

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Abbreviations: **OL**, orchidectomy plus lycopene; **CR**, complete response.

EDITORIAL COMMENT

If the results of this randomized controlled trial are not a product of chance and can be reproduced it will have a major impact on the treatment of prostate cancer. To be able to achieve a beneficial clinical and objective response and a survival advantage in M1 prostate cancer is extraordinary and to do so with an agent as innocuous as an antioxidant is even more so. All current trials, future and past, will need to account for lycopene ingestion as a confounding agent. However, there are several important considerations about the trial methods and interpretation. Was there balance in the extent of disease between the treatment arms? In a small trial imbalance is possible and the outcome differences between minimal and extensive osseous disease could account for the apparent benefit of the lycopene arm.

The dose of lycopene (4 mg/day) is significantly less than that used in studies cited in the discussion. How was a dose of 2 mg twice daily decided upon and what was the access to lycopene by the population outside the protocol? Is contamination a possibility and how was it monitored?

Lastly, I would not consider a decrease in PSA to <4 ng/mL as a biochemical complete response; such a response should reach undetectable levels (< 0.1 or <0.2 ng/mL). I am concerned with the reported complete bone scan response of 25%, as information proved in the Table indicated that no PSA level was undetectable.

Unfortunately urology has had too few clinical trials in prostate cancer issues. While there may be disagreement about clinical trial interpretation, nevertheless trials offer the best datasets upon which to generate discussion, hypothesis and future trial questions.

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