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Original article

Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer

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Abstract

Objective: In a prospective study we evaluated the efficacy of lycopene for the treatment of patients with metastatic hormone refractory prostate cancer.

Material and Methods: Between January 2001 and December 2002, 20 consecutive patients (median age 72; range 56–90) with metastatic HRPC were enrolled in the study. Lycopene in the dose of 10 mg/day was administered for a period of 3 months. Inclusion criteria were patients previously treated with hormonal therapy now with clinical and biochemical evidence of disease progression. A complete response (CR) was defined as a normalization of PSA (<4 ng/mL) and the disappearance of any sign of disease for at least 8 weeks. A partial response was defined as a >50% decrease in PSA level for at least 8 weeks associated with improvement (or no worsening) in ECOG PS and relief of bone pain if present. Stable disease (SD) was defined as a <50% decrease or <25% increase in the PSA level associated with no worsening of ECOG PS and/or bone pain for at least 8 weeks.

Results: One patient (5%) had complete response. Partial response was achieved in 6 (30%), disease remained stable in 10 (50%) and progressed in three (15%) patients. ECOG PS was Grade 0 in five, Grade I in 10 and Grade II in five of the 20 patients. It improved from Grade I to 0 in seven and Grade II to I in three patients. It deteriorated in three and remained unchanged in the rest seven patients. Bone pain was present in 16 (Grade 1 in six and Grade 2 in 10) of the 20 patients. Grade 1 changed to Grade 0 in five and Grade II changed to Grade 1 in five patients. Bone pain remained unchanged in 5 (31%) and worsened in 1 (6%). Ten (62%) patients managed to cut down the dose of analgesics on daily basis. Eighteen patients had associated LUTS, which improved (Q max ≥ 12 mL/sec) in 11 (61%) patients. The median duration of response was 25 weeks (range 12–72 weeks). No drug intolerance or toxicity was encountered in any patient.

Conclusions: Lycopene therapy appears to be effective and safe in the treatment of HRPC. It not only takes care of the rising PSA but also improves the ECOG performance status, bone pain and LUTS. Because of its relative innocuousness it should be tried before the use of more toxic substances.

Keywords: Carotenoid; Lycopene; Reactive oxygen species; Free radical; Antioxidant; Hormone resistent prostate cancer

1. Introduction

Approximately 80% of the patients of metastatic prostate cancer (PC), despite castrate levels of testosterone, progress within 12 to 18 months to an androgen-independent disease [1]. Hormone-sensitive androgen-independent prostate cancer can be treated successfully with second line hormonal manipulations like antiandrogen withdrawal, nilutamide or biclutamide. Hormone-insensitive, androgen independent or hormone refractory prostate cancer (HRPC) is unresponsive to these treatments. In such frantic situations various options like chemotherapy, ketoconazole, suramin, or newer approaches such as octreotide and growth factor inhibitors [2,3] have been tried with equivocal response. Lycopene, a carotenoid, in the recent years has emerged as unique choice in the chemoprevention and treatment of various kinds of cancers, because of its exceptional properties of cancer prevention and regression besides being the most potent quencher of free radicals and immunomodulator [4]. There are several epidemiological as well as case-control studies including one from authors' center, which have shown anticancer effect of this molecule in prostate cancer [5–8]. Though there are some case-control studies, which failed to show positive relation between lycopene intake and prostate cancer risk. These studies were not free from shortcomings

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like, small sample size and possibly lycopene degradation in sample due exposure to sunlight or long storage time [9,10]. More convincing results in recent clinical trials using lycopene are opening new avenues in the treatment of advanced or HRPC where improvement or maintenance of the quality of life (relief of bone pain and lower urinary tract symptoms) of treated patient must be the primary end point in consideration of impossibility of cure [6,8,11]. On the basis of this we did a prospective Phase II study to evaluate the clinical efficacy of lycopene in the treatment of patients with metastatic HRPC.

2. Materials and methods

Between January 2001 and December 2002, 20 consecutive patients (median age 72; range 56–90) with metastatic HRPC received lycopene therapy. Hormone resistant prostate cancer was defined as increase in PSA levels of more than twice the normal PSA value (0–4 ng/mL) confirmed in two consecutive determinations at 2-week intervals in the presence of castrate levels of testosterone [12]. Patients included in the study had earlier undergone treatment with bilateral orchiectomy and antiandrogen (flutamide 100 mg three times a day) and failed to respond to antiandrogen withdrawal. Patients who had received any other form of therapy like radiotherapy, chemotherapy, or life expectancy <3 months were excluded from the study. Preintervention evaluation included a thorough medical history, physical examination, ultrasound (KUBP), serum PSA level, radionuclide bone scan, biochemical profile, Eastern Cooperative Oncology Group performance status (ECOG PS), bone pain, recording of lower urinary tract symptoms (LUTS) and uroflowmetry. Lycopene (Lycored softules) in the dose of 10 mg/day was administered for a period of 3 months. Postintervention an assessment of S. PSA level, ECOG PS, bone pain, analgesic requirement, LUTS and uroflowmetry was done initially at 2-week intervals and later on monthly basis. Patients were also instructed to immediately report in case of any side effects or toxicity related to the drug.

2.1. Response criteria

The response criteria laid by ECOG was adopted to evaluate the results [12,13]. A complete response (CR) was defined as a normalization of PSA (<4 ng/mL) and the disappearance of any sign of disease for at least 8 weeks. A partial response (PR) was defined as a $\geq 50\%$ decrease in PSA level (confirmed in three consecutive determinations at 2 week intervals) for at least 8 weeks associated with improvement (or no worsening) in ECOG PS and relief of bone pain if present. Stable disease (SD) was defined as a $<50\%$ decrease or $<25\%$ increase in the PSA level associated with no worsening of ECOG PS and/or bone pain for at least 8 weeks. Progressive disease (PD) was defined as a $\geq 50\%$ increase in the PSA level, new sites of disease, and/or worsening of ECOG PS and/or bone pain [12,13]. For the assessment of bone pain a simplified version of "present pain intensity" scale of McGill-Melzack method was used [14]. This method includes a three-point scale; Grade 0 = no pain, Grade 1 = mild pain, and Grade 2 = severe pain. For LUTS objective assessment was done by uroflowmetery (maximum flow rate) and subjective through a questionnaire that included both irritative and obstructive features. Each feature was recorded as improved, unchanged or deteriorated. Statistical analysis was performed by log rank test and survival was calculated by Kaplan-Meier method. A P value <0.05 was taken as statistically significant.

Table 1
Patient characteristics

	No.	Percentage (%)
Evaluable patients	20	100
Age (years)		
Median	72	
Range	56–90	
Base line PSA (ng/mL)		
Median	50.10	
Range	8.2–960	
ECOG PS		
0	05	25
1	10	50
2	05	25
Bone pain		
Present	16	80
Grade I	06	37.5
Grade II	10	62.5
Absent	04	20
LUTS		
Present	18	90
Absent	02	10
Gleason score		
2–4	12	60
5–7	05	25
8–10	03	15

3. Results

Between Jan 2001 and December 2002, 20 consecutive patients (median age 72; range 56–90) with metastatic HRPC received lycopene therapy. Pretreatment patient characteristics are listed in Table 1 and postlycopene therapy status is given Table 2.

3.1. PSA changes

One patient (5%) had complete response (CR) with PSA returning to 3.6 ng/mL from 960 ng/mL. PR was achieved in 6 (30%) patients with a PSA decrease at least by 50%. Disease remained stable in 10 (50%) patients and progressed in three (15%).

Table 2
Post-lycopene therapy status at 12 weeks

	Before lycopene	After lycopene
Base line PSA (ng/mL)		
		CR-1 (5%)
Median	50.10	PR-6 (30%)
Range	8.2–960	SD-10 (50%)
		PD-3 (15%)
ECOG PS		
0	05	Remained unchanged in 4
		Grade 0 changed to Grade 1 in 1 patient
1	10	Grade I changed to Grade 0 in 7 patients
		Grade I changed to Grade 2 in 2 patients
		Remained unchanged in 1 patient
2	05	Grade II changed to Grade I in 3 patients
		Remained unchanged in 2 patients
Bone pain		
Present	16	
Grade I	06	Grade I changed to Grade 0 in 5 patients
		Worsened in 1
Grade II	10	Grade II changed to Grade I in 5 patients
		Remained unchanged in 5
Absent	04	
LUTS		
Present	18	Improved in 11 (61.11%) (Q max ≥ 12 mL/min)
		Remained unchanged in 5 (27.77%)
Absent	02	Worsened in 2 (11.11%)

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

3.2. ECOG PS

ECOG PS was Grade 0 in five, Grade I in 10 and Grade II in five of 20 patients. It improved from Grade 1 to 0 in seven and Grade II to I in three patients. It deteriorated in three and remained unchanged in the rest seven patients at minimum follow-up of 24 weeks.

3.3. Improvement in bone pain

Bone pain was present in 16 (Grade 1 in six and Grade 2 in 10) of the 20 patients. These patients required both nonopioid (nine patients) as well as opioid (seven patients) analgesics. Grade 1 changed to Grade 0 in 5 and Grade II changed to Grade 1 in five patients. Bone pain remained unchanged in five [31] and worsened in one (6%). Ten patients (62%) managed to cut down the dose of analgesics on daily basis. Of these six patients belonged to nonopioid group and four to opioid group. These 10 patients, who showed improvement in bone pain, also showed corroborative changes in their bone scans by 25 ± 5% reduction in overall meatastaic lesions on quantitative assessment.

3.4. Lower urinary tract symptoms (LUTS)

Eighteen (90%) patients had associated LUTS. The parameters recorded were both irritative (mainly frequency and urgency) and obstructive features (mainly projectile or non projectile stream and straining on micturition) and an objective evaluation was done with uroflowmetry. In 11 (61%) patients LUTS improved along with the flow rate (Q max ≥12 mL/sec), in five (28%) remained unchanged and in two (11.11%) symptoms further worsened.

3.5. Median duration of response

The median duration of response was 25 weeks (range 12–72 weeks). At a follow-up of 3 to 36 months median overall survival was 14 months (range 3–36) (Figure 1). The base line PSA and Gleason score were strongly predictive of clinical response and over all survival ($P = 0.005$ by log rank test). All seven responders (CR = 1 and PR = 6) belonged to Gleason score 2 to 4 and had PSA in between 8.2 to 20 ng/mL.

3.6. Drug intolerance

No drug intolerance or toxicity was encountered in any patient.

4. Discussion

In HRPC cure is not possible, palliative treatments such as second line hormonal manipulation or chemotherapy are recommended [15,16]. The initial step in the management of HRPC is to confirm and maintain testicular androgen suppression followed by discontinuation of nonsteroidal antiandrogen therapy [17]. A trial of observation of antiandrogen withdrawal (AAW) effect is recommended before shifting to second line hormonal therapy with antiandrogens like biclutamide or nilutamide [18]. The phenomenon of AAW has been documented in 15% to 20% of patients who had disease progression after combined androgen blockade [19]. Similarly a biochemical response rate of 14% to 29% has been reported with second line hormonal therapies. When second line hormonal therapy fails other options like chemotherapy, growth factor inhibitors or clinical trials with newer drugs come to play their roles [20]. With chemotherapy a biochemical response rate of 19% to 56% with an objective response between 14% to 35% has been reported [21–23]. But these results are not devoid of severe (Grade 3–4) haematological and nonhaematological toxicities [24]. Besides majority of these studies had a possible bias in

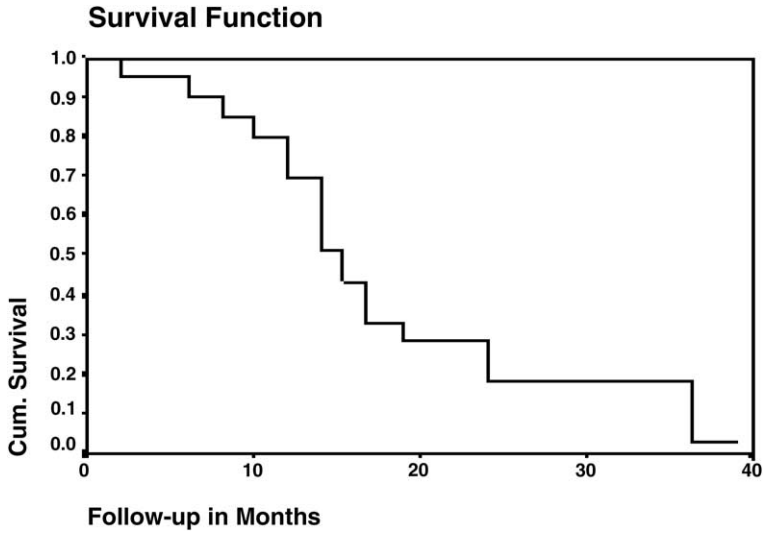

Fig. 1. Overall survival of patients at three years.

response evaluation because of the confounding use of corticosteroid a drug with a known effectivity in HRPC [25].

Over many decades there had been a continuous search to find newer drug molecules with potential effectivity and safety to provide respite to the patients of HRPC. The result of this incessant search is the drug molecule called lycopene. Lycopene is a carotenoid present in high concentration in tomatoes and tomato products [5,6]. Lycopene acts as an antioxidant and interact with reactive oxygen (singlet oxygen [$^1O_2$]) species (ROS) such as hydrogen peroxide and nitrogen dioxide. These ROS are produced during metabolism of cells and are prime candidates for DNA-damaging agents. This oxidative damage is an important event for the initiation or promotion of prostate cancer [6]. The other proposed mechanisms of action for its anticancer effect are; (1) Inhibition of cell proliferation by inhibiting autocrine growth factor such as insulin growth factor (IGF-I) that induces cell proliferation [26], (2) Inhibition of malignant transformation by up-regulation of gap junction communication resulting from the increased expression of connexin 43, a key protein forming the gap junction [27], (3) Induction of cell differentiation and apoptosis [28] and (4) intervention in cell cycle progression, i.e., slowing down of cell cycle progression at S-phase [29]. These multiple, multi-step mechanisms contribute to its consistent and superior anticancer activity over certain other carotenoids. Recently, several case-control studies have shown inverse association between serum lycopene levels and incidence of prostate cancer [6–8]. Giovannucci et al. [7] estimated lycopene intake in Health Professional Follow-Up Study (HPFS) cohort using the USDA carotinoid database. Dietary intake of lycopene (86% of which was derived from tomatoes and tomato products) was inversely related to the risk when the highest quantile (>6.5 mg lycopene/day) was compared with the lowest quantile (<2.3 mg lycopene/day, RR = 0.79, 95% Cl = 0.64–0.99, $P = 0.04$) [7]. Kucuk and colleagues [6] published more provocative clinical observations in their study involving 26 men with newly diagnosed, clinically localized (14 T1 and 12 T2) prostate cancer. The patients were randomly assigned to receive 15 mg of lycopene ($n = 15$) twice daily or no supplementation ($n = 11$) for 3 weeks before radical prostatectomy. Eleven (73%) subjects in the intervention group and 2 (18%) subjects in the control group had no involvement of surgical margins and/or extra-prostatic tissues with cancer ($P = 0.02$). Twelve (84%) subjects in the lycopene group and 5 (45%) subjects in the control group had tumors <4 mL in size ($P = 0.22$). Diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia was present in 10 (67%) subjects in the intervention group and in 11 (100%) subjects in the control group ($P = 0.05$). PSA levels decreased by 18% in the intervention group, whereas the same increased by 14% in the control group ($P = 0.25$) [6]. In the present study also 7 (35%) patients (CR = 1 and PR = 6) had a decrease in PSA levels by >50% and 10 (50%) patients had stable disease according to the criteria adopted.

Recently, Matlaga et al. [30] described a case of HRPC, which failed to respond to multiple treatment regimens finally responded to lycopene (10 mg/day) and saw palmetto (300 mg three times a day) [30]. In our study also one out of the 20 patients had a complete response (PSA < 4 ng/mL). More recently, in a prospective randomized trial we obtained superior clinical outcome and a better survival with the addition of lycopene to orchiectomy as compared to orchiectomy alone [8]. In the present study the median overall survival was 14 months (3–36), which is in agreement to the other series of HRPC, which have reported it between 2 to 18 months (range 1.3–36.7) [21,31,32]. These observations further testify the anticancer effect of this relatively innocuous molecule. Not only that on account of its effectivity and relative safety the same drug can also be

combined with other drugs with known effectivity in HRPC to get a more pronounced additive effect.

Though we could achieve modest results the present study had certain limitations like; a nonrandomized trial with small patient population and serum lycopene levels were obtained in few patients only due financial constraints. To alleviate dietary bias we tried to ensure that none of these patients was subsisting on fruits and vegetables known to have high lycopene.

Lastly, it is pertinent to discuss the dosage requirement for lycopene therapy, as the optimal dose of lycopene has not been established so far. Bohm et al. [33] showed that the intake of 5 mg of lycopene oleoresin per day resulted in 2.5-fold increase in plasma lycopene levels [33]. Giovannucci et al. [7] in their study showed that the highest quintile for lycopene intake was above 6.5 mg/day with a mean level of 10 mg/day [7]. It would be interesting to note that a plateau is achieved once the dose above 10 mg/day is administered.

5. Conclusions

Present data prove that administration of lycopene in patients with HRPC can achieve a significantly sustained PSA response along with relief in bone pain and lower urinary tract symptoms. Because of its relative innocuousness it should be tried before the use of more toxic substances. As a result of its different mechanism of action lycopene can be used in adjunct to chemotherapy or other treatment modalities available for HRPC to get a more additive and pronounced effect. Still the randomized prospective studies with large numbers of patients are required to further evaluate the possible therapeutic advantage of this worthy molecule.

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