Combination Therapy with VP16 and Ethinylestradiol for Hormone-Refractory Prostate Cancer: Good Response with Tolerability

HARUHITO AZUMA, TERUO INAMOTO, KIYOSHI TAKAHARA, NAOKAZU IBUKI, KOHEI KOYAMA, SYNYA UTIMOTO, YUTAKA FUJISUE, HIROHUMI UEHARA, KAZUMASA KOMURA, HAYAHITO NOMI, TAKANOBU UBAI and YOJI KATSUOKA

Department of Urology, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan

Abstract. *Objectives: This study evaluated the safety profile and therapeutic value of a combination therapy of etoposide and ethinylestradiol, which is a novel treatment protocol for patients with hormone-refractory prostate cancer (HRPC). Patients and Methods: Patients were given etoposide (25 mg/day, daily) and ethinylestradiol (3 mg/day, daily) orally until disease progression or unacceptable toxicity. The response rate, survival and safety profiles were evaluated. Results: Between 2003 and 2009, 61 patients were enrolled. In terms of PSA levels, >70% of patients showed a >50% reduction (complete response [CR] 51%, partial response 23%) and >90% showed a clinical response. Of 58 patients with measurable lesions, 24% (14/58) showed a CR, and most of these patients (13/14, 93%) survived without recurrence with median response duration of 28 months Conclusion: The regimen was tolerable, with a significant improvement in quality of life, and produced an effective response in patients with HRPC.*

The standard therapy for hormone-refractory prostate cancer (HRPC) has been considered to be docetaxel with prednisone or estramustine (1, 2). However, the significant toxicity of docetaxel may cause severe side-effects such as leukopenia and nausea and decrease the patient's quality of life (QOL) because of the need for hospitalisation. Other options such as bisphosphonates, mitoxantrone, and steroids, may achieve a marked improvement in both social and emotional functioning (3), but such treatments are essentially palliative and do not prolong survival. Accordingly, there is a need for a novel treatment that is well tolerated, does not decrease QOL and can prolong the survival of patients.

This study reports the results obtained with a combination therapy comprising oral ethinylestradiol and etoposide in 61 patients with HRPC.

Correspondence to: Haruhito Azuma, MD, Ph.D., Department of Urology, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan. Tel: +81 726831221, Fax: +81 726846546, e-mail: uro004@poh.osaka-med.ac.jp

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Patients and Methods

Eligibility criteria. Patients with histologically confirmed adenocarcinoma of the prostate that had relapsed after previous treatment with luteinising hormone-releasing hormone analogues and antiandrogens were enrolled. All antiandrogen therapy was discontinued for at least one month, and prostate-specific antigen (PSA) measurements were repeated to identify those patients who might benefit from antiandrogen withdrawal. Patients with evidence of rising PSA levels and/or deterioration of symptoms and radiographic abnormalities attributable to the underlying cancer were enrolled. Patients with progressive disease during single-agent ethinylestradiol therapy were eligible for entry. The scientific and ethics committees of the host institution approved the protocol and all patients provided informed consent before study entry.

Response criteria. All patients who were started on the therapy were evaluated for response. Patients who discontinued treatment for any reason and at any time were classified as non-responders. In terms of PSA, partial response (PR) required a decrease of more than 50% from the baseline PSA level but remaining over the normal range on three successive measurements 2 weeks apart; complete response (CR) required a PSA level within the normal range; progressive disease (PD) was defined as two consecutive rises from the baseline PSA level.

For patients with measurable soft-tissue disease (lung, lymph nodes, local recurrence and liver), CR required the complete disappearance of all radiographic evidence of disease for at least 4 weeks. PR required a 30% or greater decrease in the sum of the products of the perpendicular diameters of all measured lesions. Stable disease (SD) was defined as regression not meeting the above criteria for an objective response with no progression for at least 3 months. All other cases were defined as PD. For osseous disease, CR required the complete disappearance of all lesions evident in bone scans for at least 4 weeks. PR was defined as return to normal in 30% or more of the abnormal areas noted on the pretreatment

bone scan, without the appearance of new lesions. Osseous SD required the absence of new bone lesions in two bone scans taken 2 months apart. All other patients were considered to have PD.

Toxicity and QOL. Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria: Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Changes in QOL were measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire (4, 5) before and 2 months after the start of this therapy. Results were expressed as median values and 1st to 3rd quartiles (Qu). The Wilcoxon matched-pair signed rank test was used to compare differences in QOL before and after the treatment.

Treatment regimen and statistical analysis. The therapy consisted of continuous oral administration of 1 mg capsules of ethinylestradiol, 3 times a day, as well as 25 mg etoposide, once a day. Therapy was continued until bone or soft-tissue disease progression, an increase in the PSA level (two consecutive rises from a PSA nadir) or occurrence of intolerable toxicity. A 50% reduction in etoposide dose was planned for persistent gastrointestinal (GI) side-effects, and haematological toxicity. For grade ≥2 non-haematological toxicity (except for alopecia and adequately treated nausea/vomiting) and for grade ≥3 haematological toxicity, treatment was delayed until recovery (≤grade 1). Colony-stimulating factor and/or recombinant human erythropoietin-alpha were used only in instances of prolonged severe neutropaenia and anaemia, respectively. PSA and tumour measurements (by physical examination, computed tomography [CT] or magnetic resonance imaging [MRI]) were performed within 14 days after registration and subsequently every 4 weeks. Bone scans for osseous disease and CT or MRI for measurable disease were performed every 6 months. Time-to-event curves were estimated using the Kaplan-Meier method. Survival was calculated from the start of this therapy until death from any cause. The time to progression was determined as the interval between the start of therapy to the first date on which disease progression was objectively documented, a PSA rise was confirmed in two consecutive measurements or treatment was discontinued. The primary endpoint of this study was the response to chemotherapy. The secondary endpoints were survival and toxicity.

Table I. *Patient characteristics*.

	N	%	95% CI
Age (years)			
Median		70	
Range		50-86	
ECOG performance status			
0	11	18.0	9.36-30.0
1	21	34.4	22.7-47.7
2	25	41.0	28.6-54.3
3	4	6.6	1.82-15.9
Primary status			
Primary clinical stage			
B	4	6.6	1.82-15.9
C	5	8.2	2.72-18.1
D1	5	8.2	2.72-18.1
D2	47	77.0	64.5-86.8
Gleason's score			
5	1	1.6	0.04-8.8
6	0	0	0-5.87
7	18	29.5	18.5-42.6
8	8	13.1	5.84-24.2
9	30	49.2	36.1-62.3
10	4	6.6	1.82-15.9
PSA (ng/ml)			
Median	75.7		
Range	4.74-30789		
PSA-nadir			
Median	0.23		
Range	0-47.0		
At recurrence			
Measurable disease			
OS	34	47.5	31.5-63.9
LN	5	8.6	2.86-19.0
OS + LN	19	32.8	21.0-46.3
PSA (ng/ml)			
Median	15.8		
Range	1.2-1612		

95% CI: 95% Confidence interval; PSA: prostate-specific antigen; OS: osseous disease; LN: lymph node disease.

Results

Patient characteristics. Between June 2003 and December 2009, a total of 61 prostate cancer patients with relapse after previous hormonal therapies at three participating centres entered the trial. All patients were eligible for analyses on an intent-to-treat basis for response, toxicity and survival. The characteristics of the patients enrolled in this study are shown in Table I. After primary treatment with total androgen blockade (TAB), four patients received ethinylestradiol monotherapy and five had estramustine sodium phosphate (EMP) therapy, before receiving combined therapy with etoposide and ethinylestradiol.

Treatment response and outcome. Treatment response and outcome were evaluated in terms of PSA levels and measurable disease, including osseous disease and lymph node metastasis. The response and duration in each category are shown in Table II. Response rates, objective clinical responses and durations are shown in Table III.

In terms of PSA levels, 31 patients (50.8%) achieved CR with a median response duration of 25 months (range 3-71 months; 1st-3rd Qu=14-45 months), and 17 of these 31 patients (55%) showed no recurrence after a median follow-up period of 43 months (range 3-71 months; 1st-3rd Qu=25-56 months) (Table II). Fourteen patients (23%) achieved PR with a median response duration of 10 months (recurrence in 10 patients; range 3-25 months; 1st-3rd Qu=7-12 months). Ten patients showed SD (16.4%) with a median response duration of 8 months (recurrence in 8 patients; range 3-43 months; 1st-3rd Qu=6-11 months). The remaining 6 patients (8.96%) showed PD. The response rate and the clinical objective response for PSA were 73.8% and 90.2% with a

median response duration of 16 months (range 3-71 months; 1st-3rd Qu=11-29) and 14 months (range 3-71 months; 1st-3rd Qu=8-27), respectively (Table III).

Fifty-eight patients had measurable disease, including osseous disease or lymph node metastasis (osseous disease only, 34 patients; osseous disease plus lymph node metastasis, 19 patients; lymph node metastasis only, 5 patients), when diagnosed as having hormone-refractory disease.

Among the patients with osseous disease, 20.8% (11/53) achieved CR, with most of them (10/11, 91%) surviving without recurrence for a median response duration of 26 months (range, 3 to 68 months; 1st-3rd Qu=23-42 months). Seven patients (13.2%) showed PR with a median response duration of 25 months (recurrence in 3 patients; range 11-64 months; 1st-3rd Qu=16-29 months) (Table II). Twenty-eight patients (52.8%) showed SD with a median response duration of 11 months (recurrence in 19 patients; range 3-63 months; 1st-3rd Qu=8-20 months). The remaining 7 patients (11.5%) showed PD with this regimen and began palliative therapy.

In terms of lymph node metastasis, 3 patients (12.5%) achieved CR, with 2 of them surviving without recurrence with a median response duration of 57 months (range 43-71 months; 1st-3rd Qu=50-64 months). Three patients (12.5%) achieved PR with a median response duration of 14 months (recurrence in 2 patients; range 11-15 months; 1st-3rd Qu=13-15 months) (Table II). Fifteen patients (62.5%) showed SD with a median response duration of 10 months (recurrence in 14 patients; range 5-32 months; 1st-3rd Qu=7-15 months). The remaining 3 patients (12.5%) showed PD.

With regard to overall evaluation of measurable disease, 24.1% of the patients (14/58) achieved CR, with most of them (13/14, 91%) surviving without recurrence for a median response duration of 28 months (range 3 to 71 months; 1st-3rd Qu=25-46 months). Eight patients (13.8%) had PR with a median response duration of 22 months (recurrence in 4 patients; range 11-64 months; 1st-3rd Qu=15-27 months) (Table II). Twenty-nine patients (50%) showed SD with a median response duration of 10 months (recurrence in 20 patients; range 3-63 months; 1st -3rd Qu=8-20 months). With regard to objective clinical response, 51 out of the 58 patients (87.9%) showed a response (CR, 24.1%; PR, 13.8%; SD, 50.0%) with a median duration of 18 months (range 3-71 months; 1st-3rd Qu=10-28 months). Among these responders, 51% (26/51) [CR, 13/14 (92.9%); PR, 4/8 (50%); SD, 9/29 (31.0%)] survived without recurrence for a median follow-up period of 27 months (range 3-71 months; 1st-3rd Qu=16-51 months) (Table III). In terms of overall evaluation, 26.2% of patients (16/61) achieved CR, with 75% (12/16) surviving without recurrence for a median response duration of 36 months (range 3 to 71 months; 1st-3rd Qu=25-53 months). Nine patients (14.8%) had PR, with a median response duration of 15 months (recurrence in 6 patients; range 3-64 months; 1st-3rd Qu=11-25 months) (Table II). Twenty-nine patients showed SD (47.5%), with a median response duration of 11 months (recurrence in 21 patients; range 3-63 months; 1st -3rd Qu=7-20 months). The response rate was 41.0% (CR, 26.2%; PR, 14.8%), with a median response duration of 25 months (range 3-71 months; 1st-3rd Qu=11-46 months). Fifty-four out of 61 patients (88.5%; CR, 26.2%; PR, 14.8%; SD, 47.5%) showed objective clinical responses with a median response duration of 15 months (recurrence in 31 patients; range 3-71 months; 1st-3rd Qu=8-28 months) (Table III).

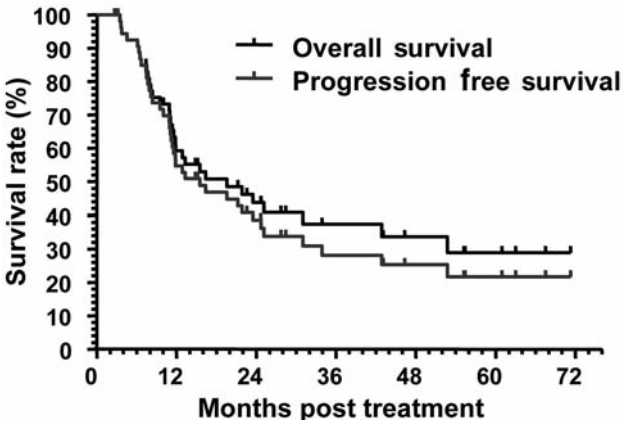

Figure 1. *Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) for all patients.*

Survival. The median progression-free survival (PFS) period after the start of this therapy was 12 months (range 0-71 months; 1st-3rd Qu=7-25 months). Twenty-three patients (37.7%; CR, 19.7%; PR, 4.9%; SD, 13.1%) survived without recurrence for a median follow-up period of 28 months (range 3-71 months; 1st-3rd Qu=15-54 months). The median overall survival (OS) period after the start of therapy was 23 months (range 3-71 months; 1st-3rd Qu=11-43 months). Twenty-six patients (42.6%) were alive at the time of writing, with more than 65% (17/26) having no recurrence within a median follow-up period of 43 months (range 3-71 months; 1st-3rd Qu=25-61 months).

The significance of each factor shown in Table IV as a predictor of PFS and OS was investigated using the Cox regression model. Univariate Cox regression analysis selected CR induction at 3 months, CR or PR induction at 3 months, PD or disease recurrence, PSA value at the nadir, PSA value at the start of therapy and metastasis to both bones and lymph nodes as significant factors predictive of both PFS and OS (Table IVa). Multivariate Cox regression analysis selected CR induction at 3 months, CR or PR induction at 3 months, PD or disease recurrence, PSA nadir and PSA value at the start of therapy as significant factors affecting both disease progression and OS (Table IVb). Figure 1 shows the Kaplan-

Table II. *Response at 3 months, response duration in months and outcome.*

	Overall	CR	PR	SD	PD
PSA (n=61)					
Number of patients, n (%), 95% CI	61 (100%)	31 (31/61,50.8%), 38-64	14 (14/61, 23%), 13-36	10 (10/61, 16.4%), 8.2-28	6/61 (9.8%), 3.7-20%
Response duration (Med, range, 1-3rdQu)	12, 0-71, 7-25	25, 3-71, 14-45	10, 3-25, 7-12	8, 3-43, 6-11	0
Survival without rec, n (%), 95% CI	23/61 (37.7%), 26-51%	17/31 (54.8%), 36-73%	4/14 (28.6%), 8.4-58%	2/10 (20%), 2.5-56%	0
Duration without rec (Med, range, 1-3rdQu)	28, 3-71, 13-54	43, 3-71, 25-56	9, 3-15, 7-12	27, 11-43, 13-54	0
Death, n (%), 95%CI	35/61 (57.4%), 44-70%	13/31 (41.9%), 25-61%	11/14 (78.6%), 49-95%	8/10 (80%), 44-98%	3/6 (50%), 12-88%
Measurable disease (n=58; osseous disease only, 34; lymph node only, 5; osseous disease+lymph node, 19)					
Number of patients, n (%), 95% CI	58/61 (95.1%), 86-99%	14/58 (24.1%), 14-37%	8/58 (13.8%), 6.2-25%	29/58 (50.0%), 37-63%	7/58 (24.1%), 10-44%
Response duration (Med, range, 1-3rdQu)	14, 0-71, 8-26	26, 3-71, 22-46	22, 11-64, 15-27	11, 3-63, 8-20	0
Survival without rec, n (%), 95% CI	26/5 (44.8%), 32-59%	13/14 (92.9%), 66-100%	4/8 (50.0%), 16-84%	9/29 (31.0%), 15-51%	0
Duration without rec (Med, range, 1-3rdQu)	27, 3-71, 16-51	28, 3-71, 25-46	25, 15-64, 18-39	20, 8-63, 11-55	0
Death, n (%), 95% CI	34/58 (58.6%), 45-71%	2/14 (14.3%), 1.8-43%	1/8 (12.5%), 3.2-53%	6/29 (20.7%), 8.0-40%	4/7 (57.1%), 18-90%
Osseous disease (n=53)					
Number of patients, n (%), 95% CI	53/61 (86.9%) 76-94%	11/53 (20.8%), 11-34%	7/53 (13.2%), 5.5-25%	28/53 (52.8%), 39-67%	7/53 (13.2%), 5.5-25%
Response duration (Med, range, 1-3rdQu)	12, 0-68, 8-25	25, 3-68, 17-37	25, 11-64, 16-29	11, 3-63, 8-20	0
Survival without rec, n (%), 95% CI	23/53 (43.4%), 30-58%	10/11 (90.9%), 59-100%	4/7 (57.1%), 18-90%	9/28 (32.1%), 16-52%	0
Duration without rec (Med, range, 1-3rdQu)	26, 3-68, 11-55	26, 3-68, 23-42	29, 19-64, 24-39	20, 8-63, 11-55	0
Death, n (%), 95% CI	35/53 (66.0%), 52-79%	2/11 (18.2%), 2.3-52%	1/7 (14.3%), 0.4-58%	6/28 (21.4%), 8.3-41%	4/7 (57.1%), 18-90%
Lymph node disease (n=24)					
Number of patients, n (%), 95% CI	24/61 (39.3%), 27-53%	3/24 (12.5%), 2.7-32%	3/24 (12.5%), 2.7-32%	15/24 (62.5%), 41-81%	3/24 (12.5%), 2.7-32%
Response duration (Med, range, 1-3rdQu)	11, 0-71, 7-17	43, 21-71, 32-57	14, 11-15, 13-15	10, 5-32, 7-15	0
Survival without rec, n (%), 95% CI	4/24 (16.7%), 4.7-37%	2/3 (66.7%), 9.4-99%	1/3 (33.3%), 8.4-91%	1/15 (6.67%), 0.2– 32%	0
Duration without rec (Med, range, 1-3rdQu)	29, 11-71, 14-50	57, 43-71, 50-64	15	11	0
Death, n (%), 95% CI	17/24 (70.8%), 49-87%	0	1/3 (33.3%), 8.4-91%	14/15 (93.3%), 68-100%	2/3 (66.7%), 9.4-99%
Overall (n=61)					
Number of patients, n (%), 95% CI	61 (100%)	16/61 (26.2%), 16-39%	9/61 (14.8%), 7.0-26%	29/61 (47.5%), 35-61%	7/61 (11.5%), 4.7-22%
Response duration (Med, range, 1-3rdQu)	12, 0-71, 7-25	26, 3-71, 19-48	15, 3-64, 11-25	11, 3-63, 7-20	0
Survival without rec, n (%), 95% CI	23/61 (37.7%), 26-51%	12/16 (75.0%), 48-93%	3/9 (33.3%), 7.5-70%	8/29 (27.6%), 13-47%	0
Duration without rec (Med, range, 1-3rdQu)	28, 3-71, 15-54	36, 3-71, 25-53	15, 3-15, 9-15	31, 8-63, 11-57	0
Death, n (%), 95% CI	35/61 (57.4%), 44-70%	4/16 (25.0%), 7.3-52%	3/9 (33.3%), 7.5-70%	24/29 (82.8%), 64-94%	4/7 (57.1%), 18-90%

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; PSA: prostate-specific antigen; 95% CI: 95% confidence interval; Med: median; Qu: quartile; Survival without rec: survival without recurrence; Duration without rec: duration without recurrence.

Table III. *Response rate, objective clinical response and duration (months).*

Response at 3 months	Pt number n (%), 95% CI	Response rate (CR+PR)			Objective clinical response		
		Number n (%), 95% CI	Response duration (Med, range, 1-3rdQu)	Pt without Rec n (%), 95% CI Duration (Med, range, 1-3rdQu)	Number n (%), 95% CI	Response duration (Med, range, 1-3rdQu)	Pt without Rec n (%), 95% CI Duration (Med, range, 1-3rdQu)
PSA (n=61)							
CR	(50.8%), 38-64%	45 (73.8%), 61-84	16, 3-71, 11-29	21/45 (46.7%), 32-62% 28, 3-71, 11-29	55 (90.2%), 80-96	14, 3-71, 8-27	23/55 (41.8%), 29-56% 28, 3-71, 13-54
PR	14 (23%), 13-36						
SD	10 (16.4%), 8.2-28						
PD	6 (9.8%), 3.7-20						
Measurable disease (n=58; Osseous disease only, 34; Lymph node only, 5; Osseous disease+lymph node, 19)							
CR	14 (24.1%), 14-37	22 (37.9%), 26-52	25, 3-71, 16-40	17/22 (77.3%), 55-92% 28, 3-71, 24-50	51 (87.9%), 77-95	18, 3-71, 10-28	26/51 (51.0%), 37-65% 27, 3-71, 16-51
PR	8 (13.8%), 6.2-25						
SD	29 (50.0%), 37-63						
PD	7 (24.1%), 10-44						
Osseous disease (n=53)							
CR	11 (20.8%), 11-34	18 (33.9%), 22-48	25, 3-68, 15-30	14/18 (77.8%), 52-94% 27, 3-68, 23-42	46 (86.8%), 75-95	15, 3-68, 9-27	23/46 (50.0%), 35-65% 26, 3-68, 15-50
PR	7 (13.2%), 5.5-25						
SD	28 (52.8%), 39-67						
PD	7 (13.2%), 5.5-25						
Lymph node (n=24)							
CR	3 (12.5%), 2.7-32	6 (25.0%), 10-47	18, 11-71, 14-38	3/6 (50.0%), 12-88% 43, 15-71, 29-57	21 (87.5%), 68-97	12, 5-71, 8-21	4/21 (19.0%), 5-42% 29, 11-71, 14-50
PR	3 (12.5%), 2.7-32						
SD	15 (62.5%), 41-81						
PD	3 (12.5%), 2.7-32						
Overall (n=61)							
CR	16 (26.2%), 16-39	25 (41.0%), 29-54	25, 3-71, 11-46	15/25 (60.0%), 39-79% 28, 3-71, 19-50	54 (88.5%), 78-95	15, 3-71, 8-28	23/54 (42.6%), 29-57% 28, 3-71, 15-54
PR	9 (14.8%), 7.0-26						
SD	29 (47.5%), 35-61						
PD	7 (11.5%), 4.7-22						

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; PSA: prostate-specific antigen; 95% CI: 95% confidence interval; Res: response; Pt number: number of patients; Med: median; Qu: quartile; Pt without Rec: patients without recurrence.

Table IV. *Predictors of survival (progression-free survival [PFS] and overall survival [OS]) evaluated by univariate (a) and multivariate (b) Cox regression analyses.*

(a) Univariate Cox regression analysis

Category	PFS		OS	
	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
CR at 3 months	5.512	0.0004	4.869	0.0031
CR or PR at 3 months	3.860	0.0001	5.451	<0.0001
CR, PR, or SD at 3 months	35.407	<0.0001	2.258	0.1307
PD/REC at present	0.072	<0.0001	0.210	0.0006
PSA value at nadir	1.043	0.0015	1.047	0.0021
PSA value at the initiation of CH	1.001	0.0055	1.002	<0.0001
CR failure at 6 months after TAB	1.812	0.3263	3.752	0.0360
Metastasis to both bone and LN	0.275	<0.0001	0.236	<0.0001
Metastasis to bone only	1.674	0.0904	1.849	0.0712
Metastasis to LN only	3.172	0.1114	5.059	0.1108
No metastasis	2.492	0.3674	1.995	0.4970
Gleason's score (>7) at primary diagnosis	0.687	0.2709	0.683	0.3110
PSA at primary diagnosis	1.000	0.9042	1.000	0.4142
Age	1.007	0.7214	1.006	0.7860
Performance status	1.070	0.6957	1.147	0.5057

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; REC: recurrence; PSA: prostate-specific antigen; CH : chemohormonal therapy; TAB: total androgen blockade; LN: lymph node.

(b) Multivariate Cox regression analysis

Category	PFS		OS	
	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
CR or PR at 3 months	2.333	0.0480	4.119	0.0108
PD/REC at present	0.011	0.0003	0.112	0.0013
PSA nadir	1.039	0.0131	1.045	0.0133
PSA value at the initiation of CH	1.001	0.0198	27.459	0.0004
CR failure to 6 months after TAB	60.438	0.0029	1.002	0.0002
Metastasis to both bone and LN	1.027	0.9821	0.579	0.6446
Metastasis to bone only	0.948	0.9614	1.158	0.8996
Metastasis at LN only	2.066	0.5704	3.720	0.3724
Gleason's score (>7) at primary diagnosis	0.979	0.9581	0.597	0.2626
PSA at primary diagnosis	1.039	0.3881	1.000	0.1055
Age	1.044	0.0518	1.026	0.2775
Performance status	0.909	0.6914	0.904	0.7133

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; REC: recurrence; PSA: prostate-specific antigen; CH: chemohormonal therapy; TAB: total androgen blockade; LN: lymph node.

Meier curves for OS and PFS, respectively. PFS and OS were 38.6% and 43.8% respectively at 2 years, and 21.7% and 28.9% at 5 years after the start of this therapy (Figure 1).

Toxicity and QOL. The 61 patients underwent continuous treatment with etoposide and ethinylestradiol and the duration of the treatment ranged from 3 months to 71 months with a median of 12 months. Grade I toxicities included granulocytopaenia in 7 patients (11.5%), anaemia in 8 (13.1%), thrombocytopaenia in 6 (9.8%), GI toxicity including anorexia in 17 (27.9%), diarrhoea in 7 (11.5%), nausea in 18 (29.5%), vomiting in 7 (11.5%), liver dysfunction in 5 (8.2%), and renal failure in 1 (1.6%). Grade II toxicities involved blood/bone marrow, and included granulocytopenia in 3 patients (4.9%), anaemia in 11 (18%), and thrombocytopaenia in 2 (3.3%). No granulocyte colony-stimulating factor or red blood cell transfusion was required in any of the patients and none of the patients showed Grade

Table V. *Toxicity.*

Toxicity	Grade 1			Grade 2			Grade 3-4		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
Blood/bone marrow									
Granurocytepaenia	7	11.5	4.74-22.2	3	4.92	1.03-13.7	0	0	0
Anaemia	8	13.1	5.84-24.2	11	18.0	9.36-30.0	0	0	0
Thrombocytepaenia	6	9.84	3.70-20.2	2	3.28	0.40-11.3	0	0	0
Gastrointestinal (GI)									
Anorexia	17	27.9	17.1-40.8	0	0	0	0	0	0
Diarrhoea,	7	11.5	4.74-22.2	0	0	0	0	0	0
Nausea	18	29.5	18.5-42.6	0	0	0	0	0	0
Vomiting	7	11.5	4.74-22.2	0	0	0	0	0	0
Liver dysfunction	5	8.20	2.72-18.1	0	0	0	0	0	0
Renal dysfunction	1	1.64	0.04-8.80	0	0	0	0	0	0

95% CI: 95% Confidence interval.

III toxicities (Table V). There were no instances of febrile GI, renal or liver toxicity. Less than 10% of patients (6/61, 9.8%) withdrew from the treatment due to toxicity or mental stress after the median treatment period of 16 months (range 8-46 months; 1st-3rd Qu=11-37 months).

The FACT-P questionnaire was used to measure QOL in the 42 patients before, and 2 months after, the start of this therapy and the two data sets were then compared. A significant improvement of the QOL score was found 2 months after the start of therapy in the following subject areas: GP1, GP 2, GP 4, GP 7 and the subtotal for physical well-being; GS1 and the subtotal for social/family well-being; GE6 and the subtotal for emotional well-being; GF2, GF7 and the subtotal for functional well-being; and total score of FACT-G, as well as P1 to P3 and the subtotal for additional concerns (Table VI). Notably, there were significant improvements in the total FACT-G score and total FACT-P score 2 months after the start of this therapy compared with those before the treatment.

Discussion

Treatment options for patients with metastatic HRPC remain limited. The median survival period is generally within the range of 7 to 16 months (2, 6-12). The benefits of mitoxantrone combined with corticosteroids have been reported in randomised trials; however, this approach has not improved OS (13). Various studies of docetaxel chemotherapy have also demonstrated good PSA responses in up to half of all patients, with an improvement of median OS to some extent (1, 2, 14, 15). However, the tolerability of these treatments has been a matter of concern, particularly as most patients are elderly and many have other medical problems. Because of toxicities such as bone marrow toxicity with granulocytopenia or anaemia in more than 50% of patients (1, 2, 16), many patients cannot receive the treatment continuously, resulting in disease recurrence (1, 2, 13, 17-19). Other options such as bisphosphonates, mitoxantrone and steroids may be of palliative benefit with a marked improvement in social and emotional functioning, but do not improve patient survival (3, 20, 21). Therefore, a novel regimen with improved treatment activity in terms of both response rate and response duration is necessary for HRPC patients. With the aim of identifying active agents with a better safety profile than docetaxel- or mitoxantrone-based therapy, yet showing good activity and, thus, allowing docetaxel administration to be delayed, HRPC patients were treated with a combination of ethinylestradiol and etoposide, both being administered orally.

In the present study, this oral treatment produced an extremely high response rate with prolonged response duration. For measurable disease, 51 out of 58 patients (87.9%) showed an objective response within a median response duration of 18 months, with more than half of them (26/51, 51.0%) surviving without recurrence within a median follow-up period of 27 months. With regard to PSA levels, 31 out of 61 patients (50.8%) achieved CR with a median response duration of 25 months, with 17 out of these 31 patients (55%) having shown no recurrence to date, after a median follow-up period of 43 months. Such a high ratio of CR induction without recurrence, especially in patients with measurable disease as well as elevated PSA levels, may have contributed to the favourable rates of OS. The OS rate was 28.9% at 5 years after the start of this therapy and the median OS period after the diagnosis of HRPC was 24 months, in comparison with the literature reported figures of less than 15% and within the range of 7 to 16 months, respectively (2, 7-12, 22, 23).

In addition, it is noteworthy that the toxicity due to this treatment was markedly lower than other docetaxel- or mitoxantrone-based chemotherapy in terms of both frequency and grade. No patients suffered any category of Grade III

Table VI. *Quality of life (QOL) changes between before and after the treatment analysed by FACT-P.*

Statement	Pre-treatment	Post-treatment	*p*-Value
Well being			
Physical well-being			
GP1	3, 3-3	3, 3-4	*0.0367
GP2	3, 3-4	3, 3-3	*0.0281
GP3	3, 2-3.75	3, 3-4	0.2477
GP4	2, 1-3	3, 2.25-4	*<0.0001
GP5	3, 3-3.75	3, 3-3	0.5701
GP6	3, 2-3	3, 2-3	0.6356
GP7	3, 3-4	3, 3-4	*0.0469
Subtotal	20, 18-21.75	21, 20-23	*0.0011
Social/Family			
GS1	2, 2-3	3, 2-4	*0.0117
GS2	3, 2-3	3, 2-3	0.5751
GS3	3, 2-3	3, 3-4	0.0972
GS4	2, 2-3.75	3, 2-4	0.3525
GS5	3, 2-3	3, 2-3.75	0.0754
GS6	3, 2-3	3, 2-4	0.0929
GS7	1, 0-3	1, 0-3.75	0.2367
Subtotal	18.5, 16.25-20	19, 17-21.75	*0.0146
Emotional			
GE1	3, 2-3	3, 2-3	0.0593
GE2	2, 2-3	3, 2-4	0.0665
GE3	3, 2-3	3, 2-4	0.4755
GE4	3, 3-3	3, 3-3.75	0.1763
E5	3, 2-3	3, 2-4	0.1961
GE6	3, 2-3	3, 2-3	*0.0035
Subtotal l	17, 15-18	18, 16-19	*0.0180
Functional			
GF1	3, 2-3	3, 3-4	0.9165
GF2	3, 2-3	3, 2-4	*0.0277
GF3	3, 2-3	3, 2-4	0.0929
GF4	3, 2-4	3, 3-4	0.0917
GF5	3, 2-3	3, 2-4	0.4185
GF6	3, 2-4	3, 2-4	0.4185
GF7	3, 2-4	3, 3-4	*0.0357
Subtotal	20.5, 19-22	21, 19.25-23.75	*0.0045
FACT-G Total	75.5, 69.25-78	78, 72-83.75	*<0.0001
Additional concerns			
C2	3, 2-3	3, 2-3	0.1097
C6	3, 2-3.75	3, 2-4	0.2049
P1	2, 1-3	3, 2-3	*0.0002
P2	2, 1-3	2, 2-3	*0.0021
P3	2, 1-3	2.5, 2-3	*0.0016
P4	2, 1.25-3	3, 2-3	*0.0047
P5	3, 2-3	3, 2-3.75	0.0747
P6	3, 2-4	3, 2-4	0.4990
P7	2, 2-3	2, 2-3.75	0.7670
BL2	3, 2-4	3, 2-4	0.4498
P8	3, 2-3	3, 2-4	0.3452
BL5	0, 0-0	0, 0-0	0.6547
Subtotal	28, 24.25-30.75	30, 27-34	*<0.0001
Total score	104, 93.25-108.75	108.5, 103-115.75	*<0.0001

Quatile results are expressed as median, 1st-3rd. The Wilcoxon matched-pair, signed rank test was used to analyse QOL changes between before and after the treatment.

toxicity; Grade II toxicities such as granulocytopenia, anaemia and thrombosis were minimal, being observed in 4.9%, 18% and 3.3% of patients, respectively. Recognising the potential impact of this therapy in terms of toxicity, the effect of this treatment on QOL was also assessed using FACT-P, which is a disease-specific QOL instrument for patients with prostate cancer (4, 5). The results demonstrated the significant improvement in some categories or no decrease in others, after the treatment in comparison with the pretreatment situation. Most of the patients continued the treatment with good compliance, although 6 patients (9.8%) withdrew from the treatment due to toxicity, mental stress or aging after a median treatment period of 15 months (range 8-46 months). Thus, this safe and effective treatment regimen appears to be a new strategy for patients with HRPC. It can be a practical treatment in patients for whom intense chemotherapy is indicated, but also for patients showing disease recurrence or PD after a period of this low-toxicity treatment, OS may be prolonged by adding this treatment prior to docetaxel-based intense chemotherapy. Moreover, this can be a good treatment option for patients whose condition is not amenable to curative therapy and for whom palliative treatment would otherwise seem the only option. This regimen is clinically promising for the treatment of patients with HRPC, most of whom are elderly.

Conclusion

The combination therapy comprising oral ethinylestradiol and etoposide showed a significant effect on HRPC, inducing a high objective clinical response ratio (CR, 20%; PR, 20%; SD, 50%) as well as a prolonged response duration: more than 80% of patients (13/16, 81.3%) who achieved CR survived without recurrence within a median response duration of 28 months (range 3 to 71 months; 1st-3rd Qu=25-53 months). These good responses were accompanied by a favourable profile of well-manageable side-effects, including only mild decreases of blood leukocytes and mild anaemia, mostly related to oral etoposide administration. These favourable data suggest that this combination therapy merits further testing in clinical trials for patients with HRPC in comparison with other salvage chemotherapies or second-line hormonal therapies.

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