Ethinylestradiol Improves Prostate-specific Antigen Levels in Pretreated Castration-resistant Prostate Cancer Patients

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Abstract. Background: Ethinylestradiol was used as palliative treatment for patients with advanced prostate cancer (PCa). However, its use has declined after the development of combined androgen blockade. In the present study, we analyzed the effects of ethinylestradiol on pretreated castration-resistant PCa patients. Patients and Methods: Twenty-four Japanese patients were orally administered ethinylestradiol at a dose of 1.5 mg/day and prostate-specific antigen (PSA) was examined. We retrospectively analyzed the proportion of patients achieving a decline in PSA of >50% and progression-free and overall survival rates. Results: All patients had already been treated with combined androgen blockade followed by one or more salvage therapies. Median follow-up time was 227 (range: 42-1490) days and median ethinylestradiol treatment time was 195 (range: 3-791) days. The proportion of patients achieving a decline in PSA >50% was 70%. Median progression-free survival was estimated as 300 days. At the end of the follow-up period, one patient had died from PCa. Adverse events occurred in three patients, namely elevation of liver enzymes, anorexia, and heart failure in one patient each. Conclusion: Oral ethinylestradiol administration may be useful for treatment of advanced castration-resistant PCa after salvage therapy with a high PSA response rate and low adverse event rate.

Prostate cancer (PCa) is the most frequently diagnosed cancer in men and the second leading cause of cancer-related death in the USA. About 192,280 men (25.1% of male cancer cases) were estimated to have PCa in 2009 (1). In Europe, about 382,000 men (11.9% of all cancer) were diagnosed with prostate cancer in 2008 (2). Although hormone therapy is useful for advanced PCa, its effects are limited because PCa changes to an androgen-independent phenotype over several years of therapy (3, 4). Recently, oral salvage therapies, e.g. alternative antiandrogens, estramustine phosphate (EMP), dexamethasone, and tranilast for castration-resistant PCa (CRPCa), have been reported (5-9). However, as their effects do not last for a long time, new agents are required for treatment of advanced CRPCa. Although docetaxel-based regimens were developed as standard chemotherapy for CRPCa, high incidences of adverse events were reported for these regimens (10, 11). Treatment with ethinylestradiol was used as palliative therapy in patients with advanced PCa in the 1980s. However, ethinylestradiol treatment has become less common since the introduction of new forms of treatment, such as antiandrogens and luteinizing hormone-releasing hormone agonists (12). One reason for this decline in use is the risk of cardiovascular events during treatment with estrogens. However, ethinylestradiol treatment is inexpensive and well-tolerated, and increases survival rate in patients with metastatic PCa (13). A small study of 1 mg oral ethinylestradiol combined with lanreotide acetate for CRPCa patients showed a decline in prostate-specific antigen (PSA) of >50% in 9 out of 10 patients (14). Although ethinylestradiol may be promising for treatment of CRPCa, there have been no reports regarding treatment with ethinylestradiol alone for CRPCa patients treated with more than one salvage therapy. In the present study, we analyzed the effects of ethinylestradiol in such pretreated CRPCa patients.

Patients and Methods

Patients with CRPCa in whom more than one salvage therapy had not been effective were orally administered ethinylestradiol at a dose of 1.5 mg/day at Kanazawa University Hospital and associated institutions from October 2005 to May 2010. All patients had histologically confirmed adenocarcinoma of the prostate. Other new treatments were not started concomitant with ethinylestradiol except...
in one patient who received simultaneous zoledronic acid infusion. Additional treatments were started or ethinylestradiol was discontinued when the physician in charge judged that the state of the PCa had deteriorated despite ethinylestradiol treatment or adverse events occurred. The primary study objective was determination of the proportion of patients achieving a decline in PSA >50% according to the Prostate Specific Antigen Working Group 1 criteria (PSA response) (15). The maximal decline was determined based on the value obtained >4 weeks after commencement of treatment. Time to PSA progression was calculated for patients with PSA decline >50% from baseline at the time the PSA had increased to 50% above the nadir and was >5 ng/ml. For those not meeting the PSA decline criteria, time to PSA progression was the time at which PSA had increased by 25% from baseline.

Statistical analysis was performed using commercially available software (Prism; GraphPad Software, Inc., San Diego, CA, USA). The crude probabilities of progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. To exclude the effects of other treatments, when PFS was calculated, we regarded the time at which other new treatments were started as the time when the follow-up should end.

Results

Patient population. Twenty-four patients were enrolled in the present study. The median age and the median PSA at commencement of ethinylestradiol treatment were 75 (range: 58–86) years and 63.8 (range: 1.6–735) ng/ml, respectively. The median follow-up period after starting ethinylestradiol and the median ethinylestradiol administration period were 227 (range: 42-1490) days and 195 (range: 3-791) days, respectively (Table I). On starting ethinylestradiol, 20 patients (83%) had bone metastasis, 10 patients (42%) had lymph node metastasis, 8 patients (33%) had both bone metastasis and lymph node metastasis, and only 2 patients (8%) had no metastasis. Before starting ethinylestradiol, all patients underwent combined androgen blockade by either medical castration using luteinizing hormone-releasing hormone agonist or surgical castration with oral administration of anti-androgens, and subsequently one or more salvage therapies were given. Docetaxel-based chemotherapy was given in only 3 patients (13%). Fosfestrol and EMP were given in 2 (8%) and 21 patients (88%), respectively (Table I).

PSA change. One patient was excluded from the analysis because of withdrawal of ethinylestradiol due to elevation of liver enzymes 3 days after starting ethinylestradiol treatment. PSA responses after starting ethinylestradiol treatment are shown in Figure 1. The number of patients achieving a decline in PSA >50% was 16 (70%). The number of patients with PSA decline compared with baseline was 21 (91%). The patient who underwent both zoledronic acid infusion and ethinylestradiol treatment simultaneously showed a 69% decline in PSA. Two patients who received fosfestrol as prior treatment had declines of 72% and 51% in PSA. Three patients who did not undergo EMP showed 90%, 69%, and 28% declines in PSA. Two of the three patients who underwent docetaxel-based chemotherapy showed declines of 60% and 57% in PSA, and one patient was excluded due to elevation of liver enzymes.

PFS and OS. Median PFS was estimated after 300 days (Figure 2A). Five out of six patients who underwent other new treatments in addition to ethinylestradiol had PSA progression before starting new treatments. At the end of the
follow-up period, 22 out of 23 patients (96%) were alive and one patient had died from PCa (Figure 2B).

Additional and subsequent treatment. After starting ethinylestradiol, other treatments were started in 11 patients (48%). Only 5 (22%) patients underwent docetaxel-based chemotherapy (Table II).

Adverse events. Adverse events occurred in three patients, namely elevation of liver enzymes, anorexia, and heart failure in 1 patient each. The patient who had elevation of liver enzymes has been mentioned already. Ethinylestradiol was withdrawn 56 days after starting ethinylestradiol in the patient who had heart failure, and the dose of ethinylestradiol was decreased to 1.0 mg daily in the patient who had anorexia. Each adverse event was improved after withdrawal or a decrease in dose of ethinylestradiol.

Discussion

It is extremely difficult to cure CRPCa and there is no clear consensus regarding the appropriate management strategy. Yagoda et al. reported that among 1001 men with CRPCa who had received treatment in 26 chemotherapy trials, the objective response rate was only 8.7% and the median survival time was 6-10 months, with no clear survival benefit for any agent (16). Subsequently, two large randomized studies of chemotherapy including docetaxel for CRPCa were reported. The median survival time of CRPCa patients treated with 75 mg/m² docetaxel (DTX) every 3 weeks and daily prednisone was 18.9 months (TAX 327) (10), and the median survival time with 60 mg/m² DTX every 3 weeks and daily EMP on days 1 through 5 was 17.5 months (Southwest Oncology Group 9916; SWOG 9916) (11). These DTX-based chemotherapy regimens significantly lengthened the OS compared with the control regimen of mitoxantrone and prednisone, and was accepted as the standard form of therapy for advanced CRPCa. However, the incidence of adverse events, such as grade 3 and 4 neutropenia, was relatively high. Therefore, it was necessary to develop new agents for
treatment of advanced CRPCa. Ethinylestradiol treatment was reported to cause considerable cardiovascular events; however, comparable rates were reported in some studies following placebo treatment of patients with PCs (12). In the present study, the proportion of patients showing a PSA response >50% was 70% and the median PFS was estimated to be 300 days. The proportion of PSA response >50% was reported to be 45% in TAX 327 and median PFS was reported to be 6.3 months in SWOG 9916. These data suggest that ethinylestradiol treatment may be more beneficial than DTX-based chemotherapy. Moreover, only one cardiovascular event (heart failure) occurred in the present study, and ethinylestradiol treatment was successfully continued in 22 out of 24 patients (92%). The incidence of cardiovascular events in ethinylestradiol treatment may be lower than previously thought, and its safety and tolerability should be re-examined. However, care should be taken in comparing the present study with TAX 327 and SWOG 9916. The results of this comparison may not be correct because of the differences in background between the present study and both TAX 327 and SWOG 9916. The baseline median PSA levels in TAX 327 and SWOG 9916 were higher (84 and 114 ng/ml, respectively) than that in the present study (63.8 ng/ml). The lower baseline median PSA level in the present study may be a preferential factor regarding PSA response, PFS and OS. On the other hand, the median ages in the present study, TAX 327, and SWOG 9916 were 75, 68, and 70 years, respectively. In addition, the proportion of cases with Gleason's score 8-10 (and poor differentiation) in the present study was higher (46%) than that in TAX 327 (31%). These data suggest the advantage of ethinylestradiol.

Furthermore, ethinylestradiol had antitumor effects in CRPCa patients who have experienced treatment failure with DTX-based chemotherapy. The proportion of PSA response >50% in phase 2 studies of abiraterone acetate, which is a selective inhibitor of CYP17, and MDV3100, which is an androgen-receptor antagonist, was reported to be 36% and 56%, respectively (17, 18). Ethinylestradiol may be a useful candidate for salvage treatment after failure of treatment with DTX-based chemotherapy. Interestingly, ethinylestradiol also had antitumor effects in CRPCa patients who had experienced treatment failure with estrogens, such as fosfestrol and EMP. It was reported previously that estrogens had a direct toxic effect on PCs by induction of apoptosis in addition to an indirect antitumor effect on these cells by down-regulation of serum testosterone level (19). There may be some differences between ethinylestradiol and other estrogens in the mechanisms of their direct effects on PCs. Based on these data, ethinylestradiol may be an effective treatment with reasonable tolerability in patients with advanced CRPCa.

The present study had some limitations. It was a retrospective study with one arm. Moreover, short follow-up and small sample size may have prevented determination of the precise PFS and OS, and the incidence of adverse events. All patients were Japanese, so ethinylestradiol may not have the same effects in patients from other ethnic backgrounds. In particular, cardiovascular events may be different between races. Larger international prospective studies with longer follow-up periods are needed to confirm our findings.

Finally, although a decline in PSA >50% was achieved by ethinylestradiol in 16 out of 23 patients, a continuous increase in PSA was observed in two patients. It was unclear which factor(s) contributed to the good response to ethinylestradiol. Both the search for biomarkers that can predict the response to ethinylestradiol and examination of the differences between the mechanisms of action of ethinylestradiol and other estrogens for CRPCa are needed. Although this was a pilot study, the results suggested that ethinylestradiol could achieve a high PSA response rate and reasonable PFS and OS in patients with pretreated advanced CRPCa with a low adverse event rate.

References


