Preliminary Results of Tranilast Treatment for Patients with Advanced Castration-resistant Prostate Cancer

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Abstract. *Background: Tranilast is a therapeutic agent used in treatment of allergic diseases. It has been reported previously that tranilast has antitumour effects on prostate cancer cells. This study examined whether tranilast has clinical benefit for prostate cancer patients. Patients and Methods: Twenty-one Japanese patients with advanced castration-resistant prostate cancer (CRPC) were administered tranilast orally. Results: All patients had already been treated with combined androgen blockade followed by one or more salvage therapies and their prostate-specific antigen (PSA) continued to increase before starting tranilast. Median follow-up time was 14 months and median tranilast treatment time was 5 months. PSA progression was inhibited in 5 CRPC patients with bone metastasis. The survival rates at 12 and 24 months were 74.5% and 61.5%, respectively. Conclusion: Although this study involved only pilot data, it indicates that tranilast may improve the prognosis of patients with advanced CRPC.*

Prostate cancer (PCa) is the most frequently diagnosed cancer in men and the second leading cause of cancer-related death in the United States. About 192,000 men were estimated to have PCa in 2009 (1). 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 (2, 3). Recently, some oral salvage therapies, such as alternative anti-androgens,

estramustine phosphate (EMP), and dexamethasone (DEX) for castration-resistant PCa (CRPC) have been reported (4-6). However, as their effects are short-lived, new agents are required for the treatment of advanced CRPC. It has been reported previously that tranilast had antitumour effects for PCa cells *in vitro* and *in vivo* (7). Tranilast was originally developed as an anti-allergic drug for either systemic or topical treatment of bronchial asthma, atopic dermatitis, and allergic conjunctivitis. Its usefulness in such applications is derived from its pharmacological ability to inhibit the release of chemical mediators from mast cells and to consequently suppress hypersensitivity reaction. Tranilast has also been reported to have antitumour effects in several types of tumour cell, such as uterine leiomyoma, breast cancer, gastric cancer, oral cancer, and malignant glioma, through various different mechanisms (8-12). Despite these observations and the minimal clinical toxicity of tranilast, there have been no clinical reports regarding treatment of cancer patients with tranilast. It has also been reported that prostate-specific antigen (PSA) was temporarily reduced by oral tranilast administration in 4 out of 16 CRPC patients. However in that study, the follow-up period was short, and overall survival and additional or subsequent treatments for PCa after starting tranilast were not clarified. The present study extended this earlier series to include 21 patients with prolonged follow-up, and allowed description of additional or subsequent treatments after starting tranilast and analysis of overall survival.

Patients and Methods

Patients with CRPC in whom several salvage therapies had been ineffective were administered tranilast orally at a dose of 300 mg/day at Kanazawa University Hospital and associated institutions. All patients had histologically confirmed adenocarcinoma of the prostate. Patients were required to have adequate renal, hepatic, and haematological function and an Eastern Cooperative Oncology Group performance status of 0-3 (13). Before starting tranilast

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Table I. *Characteristics of 21 patients with advanced CRPC.*

Median age at diagnosis (year)	67 (57-88)
Median PSA (ng/ml) at diagnosis	205 (4.8-4370)
Median age at starting tranilast	74 (57-88)
Median PSA (ng/ml) at starting tranilast	16 (0.39-2079)
Median months from diagnosis to starting tranilast	45 (12-90)
Median months follow-up	14 (2-37)
Median months tranilast administration	5 (2-25)
Gleason score	
<7	2
=7	8
>7	11
T stage	
T1-2	3
T3-4	18
Metastasis	
Lymph node	10
Bone	18
Prior treatment	
Radical prostatectomy	2
CAB	21
1st AA	15
2nd AA	4
EMP	15
Ethinylestradiol	2
Dexamethasone	8
Prednisolone	3
Bisphosphonate	9
Docetaxel	1
Other chemotherapy	2
Radiation	2

CAB, Combined androgen blockade; AA, alternative anti-androgen therapy; EMP, estramustine phosphate. Data in parentheses are ranges.

Table II. *Additional and subsequent treatment.*

No		8
Yes	EMP	2
	Ethinylestradiol	4
	Dexamethasone	4
	Prednisolone	3
	Bisphosphonate	6
	Docetaxel	7
	Other chemotherapy	1
	Radiation	5

The median follow-up period after starting tranilast and the median tranilast administration period were 14 (range: 2-37) months and 5 (range: 2-25) months, respectively. Eleven patients (52%) presented with Gleason's score 8-10, 18 patients (86%) presented with locally advanced status of T3-4, and 18 patients (86%) had bone metastasis. Eight patients had both bone metastasis and lymph node metastasis. Before starting tranilast, all patients underwent combined androgen blockade (CAB) 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 (DTX) was given in only one patient. Bisphosphonate (incadronate or zoledronate) infusion was performed in patients with bone metastasis to treat or prevent skeletal-related events. Radiation therapy was also performed to improve bone pain caused by bone metastases (Table I).

Additional and subsequent treatment. After starting tranilast, other treatments were newly started in 13 patients (62%). Most of these treatments were started as additional therapy to tranilast. Seven of these 13 patients underwent DTX therapy (Table II). As well as prior treatment, zoledronate and radiation therapy were performed for 6 and 5 patients with bone metastasis, respectively.

PSA change. PSA changes before and after starting tranilast are shown in Figure 1A. Data are taken from the time PSA began to increase to the time additional treatment was started (if tranilast was continued) or tranilast was discontinued. PSA elevation was inhibited in 5 (24%) patients (for 13, 10, 4, 1, and 1 months, respectively). Three of these 5 patients had continuous stable disease and their profiles are shown in Table III.

Overall survival. At the end of the follow-up period, 14 out of 21 patients were alive. Overall survival rates at 12 and 24 months were 74.5% and 61.5%, respectively (Figure 1B).

Adverse events. Adverse events occurred in two patients: elevation of liver enzymes and headache in one patient each (Grade 1 of National Cancer Institute-Common Terminology
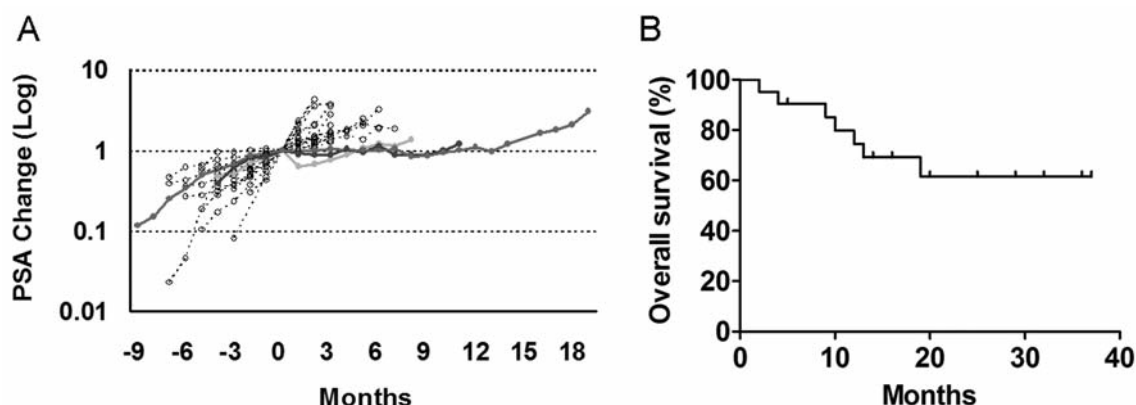
treatment, PSA levels were confirmed to have increased continuously at least 2 (3 patients) or 3 times, despite the patient having received one or more salvage therapies. Other new treatments were not started concomitant with tranilast. Physical examinations and blood tests, including PSA, were undertaken once a month. Additional treatments were permitted or tranilast was discontinued when the consulting physician judged that the state of the PCa had deteriorated despite tranilast treatment or adverse events had occurred. Stable disease was defined as the condition in which PSA level was lower than that when tranilast was started. The crude probability of survival was estimated using the Kaplan-Meier method. Studies were performed after receiving approval from the Institutional Review Board of the Graduate School of Medical Science, Kanazawa University, and after the patients gave their informed consent.

Results

Patient population. Twenty-one patients were enrolled in the study. The median age and the median PSA at starting tranilast were 74 (range: 57-88) years and 16 (range: 0.39-2,079) ng/ml, respectively. The median period from diagnosis to starting tranilast was 45 (range: 12-90) months.

Figure 1. *A: Logarithmic PSA changes in all cases are shown. PSA level was compared with that at the time of starting tranilast. All lines start from the time PSA began to increase to withdrawal of tranilast or to addition of other treatments. The three different colored solid lines show the PSA changes in effective cases. B: Kaplan-Meier analysis of overall survival in all cases is shown.*

Table III. *Profiles of tranilast effective three patients.*

	Case 1	Case 2	Case 3
Age at diagnosis (years)	72	54	73
PSA (ng/ml) at diagnosis	78.9	481	24.7
Age at starting tranilast	80	57	80
PSA (ng/ml) at starting tranilast	670	107	16.0
Months from diagnosis to starting tranilast	89	33	88
Months follow-up after starting tranilast	19	34	25
Months tranilast administration	19	20	25
Months PSA inhibition	13	10	4
Nadir PSA (ng/ml) after starting tranilast	560	93.4	10.0
Gleason score	6	9	9
TNM classification*	T3aN0M1b	T3aN0M1b	T4N0M1b
Prior treatment	CAB	CAB	CAB
	1st AA	Ethinylestradiol	1st AA
	Bisphosphonate	EMP	2nd AA
	Dexamethasone		EMP
	EMP		Dexamethasone
	Prednisolone		
	Tegafur uracil		
Additional and subsequent treatment	None	UFT	Docetaxel
		Docetaxel	Bisphosphonate

CAB, Combined androgen blockade; AA, alternative anti-androgen therapy; EMP, estramustine phosphate, UFT, florafurt+uracil. *UICC 1997.

Criteria for Adverse Events version 3.0). Each adverse event was improved immediately after withdrawal of tranilast.

Discussion

It is extremely difficult to cure CRPC and there is no clear consensus regarding the appropriate management strategy. Yagoda *et al*. reported that, among 1001 men with CRPC 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 of the agents trialled (14). Subsequently, two large randomised studies of chemotherapy including DTX for CRPC were published. It was reported that the median survival time for CRPC patients treated with 75 mg/m^2 DTX every 3 weeks and daily prednisone was 18.9 months (TAX 327) (15), and that the median survival time for those treated with 60 mg/m^2 DTX every 3 weeks and daily EMP on day 1 through 5 was 17.5 months (Southwest Oncology Group 9916; SWOG 9916) (16). These DTX regimens were able to

significantly lengthen the overall survival compared with the control regimen of mitoxantrone and prednisone, and were accepted as the standard form of therapy for advanced CRPC. However, adverse events, such as grade 3 and 4 neutropenia, were relatively high. Moreover, in Japan, DTX was not formally permitted for CRPC until 2008. Therefore, it was necessary to develop new agents for treatment of advanced CRPC.

In a previous study, it was demonstrated that tranilast inhibited PCa cell proliferation through induction of apoptosis and cell cycle arrest, and that in an osteoblastic metastasis model tranilast also inhibited transforming growth factor (TGF)-β1 production from bone stromal cells (7). TGF-β1 promotes osteoblastic change. In addition, following that study, Sato *et al*. reported that tranilast suppresses rat PCa growth and osteoclast differentiation (17). Osteoclasts, as well as osteoblasts, play an important role in the early phase of osteoblastic bone metastasis of PCa (18), thus lending theoretical support to the present study.

In the present study, continuous PSA inhibition was observed in three patients (14%), and it lasted for 4-13 months. On the other hand, no apparent PSA inhibition was observed in 16 patients (76%). It was concluded in the previous study (7) that tranilast may function as a cytostatic rather than a cytotoxic agent because the attainable serum concentration of tranilast reaches 30-300 μmol/l *in vivo* after oral administration of 600 mg/day tranilast (19). The administered dose of tranilast may be too low to overcome multiple metastases. However, overall survival rates at 12 and 24 months in the present study were 74.5% and 61.5%, respectively. Although overall survival rates at 12 months in TAX 327 and SWOG 9916 were almost equivalent to the overall survival rate at 12 months in the present study, overall survival rates at 24 months were at most 30%-40% (15, 16). These data suggest that tranilast may be more beneficial than DTX regimens. 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 TAX 327 or SWOG 9916. The median baseline PSA levels in TAX 327 and SWOG 9916 were higher (84 and 114 ng/ml, respectively) than that in the present study (16 ng/ml, however, the mean baseline PSA was 174 ng/ml). The lower median baseline PSA level in the present study may be a preferential factor in the overall survival rate at 24 months. The proportion of patients with bone metastasis in the present study, TAX 327, and SWOG 9916 was 85%, 84%, and 90%, respectively. This is in agreement with the report that skeletal metastases occurred in approximately 80% of patients with advanced PCa (20). However, the proportion of Gleason's score 8-10 in the present study was higher (52%) than that in TAX 327 (31%). In addition, 43% of patients had already been given dexamethasone alone, prednisolone alone, or both

agents before starting tranilast. Although additional and subsequent treatment after starting tranilast was performed for 62% of patients in the present study, DTX was given to only 33% of patients.

Matsumoto *et al*. reported a series of 46 Japanese CRPC patients treated with 35 mg/m^2 of DTX twice every 3 weeks and EMP for 3 consecutive days during weeks 1 and 2 of each cycle (21). In their study, the median baseline PSA was slightly higher (26.3 ng/ml) than that in the present study but was lower than those in TAX 327 and SWOG 9916. The proportion of patients with Gleason's score 8-10 in their study was higher (47.8%) than that in TAX 327, but was almost equivalent to that in the present study. The median survival time was 27.0 months, and the overall survival rates at 12 and 24 months were about 80% and 65%, respectively. However, grade 3 or 4 leukopenia was seen in 5 patients (10.8%). Tranilast has been shown to have only minor clinical toxicity, such as cystitis and hepatitis. Naturally, adverse events were grade 1 elevation of liver enzymes and grade 1 headache in the present study. Based on these data, tranilast may be an effective treatment with reasonable tolerability in Japanese advanced CRPC patients.

Tranilast may also be a useful chemical agent for combination therapy with chemotherapy or other salvage therapies. Murahashi *et al*. reported that tranilast increased the cisplatin response on OCUM-2M scirrhous gastric cancer cells (22). Yatsunami *et al*. also reported that tranilast in combination with adriamycin, cisplatin, vindesine, or cyclophosphamide suppressed the tumour growth of Lewis lung carcinoma cells more strongly than each agent alone (23). Recently, Fan *et al*. reported that tranilast may be able to enhance the anti-tumour effects of romidepsin (FK228, depsipeptide), a unique cyclic depsipeptide with histone deacetylase inhibitor activity, in bladder cancer cells (24). DTX has also been combined with several agents, including calcitriol, capecitabine, bevacizumab, and thalidomide (25). Tranilast combined with DTX may have a beneficial effect.

The present study had some limitations. It was performed as an open-label study with one arm. Moreover, short follow-up and small sample size may have prevented determination of the precise overall survival rate and incidence of adverse events. All patients were Japanese, so tranilast may not have the same effects in patients from other ethnic backgrounds. Larger prospective studies with longer follow-up periods are needed to confirm the current findings.

Finally, three patients in whom PSA elevation was continuously inhibited by tranilast had both bone metastasis and locally advanced lesions. However, it was unclear which factors contributed to the good response to tranilast. Although this was a pilot study with a short follow-up period and small sample size, the results suggested that in patients with advanced CRPC treated with tranilast may achieve an acceptable survival time.

Oral tranilast administration, which did not markedly reduce PSA level, may be useful for treatment of advanced CRPC after salvage therapies with an acceptable survival rate and low adverse event rate.

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