that the initial tumor size would be inversely associated with the tumor size reduction rate. In the present study, we investigated the relationship between the initial tumor size and the tumor size reduction rate of patients treated with TKIs.

MATERIAL AND METHODS

Patient and Treatment

The data from 139 metastatic and 16 primary lesions treated with targeted therapeutics were retrospectively analyzed. They consisted of 86 sunitinib-treated and 69 sorafenib-treated lesions from 54 patients with mRCC who had undergone treatment at our hospital from April 2008 to July 2010. Each patient signed an institutional review board-approved protocol-specific informed consent form in accordance withnational and institutional guidelines. Sunitinib was administered orally at a dose of 50 mg/d, consistingof 4 weeks of treatment followed by a 2-week rest period. Sorafenib was administered orally at a continuous dose of 800 mg/d. Dose reductions of sunitinib (to 37.5 mg and then to 25 mg) and sorafenib (to 400 mg/d and then to 400 mg every other day) were performed, depending on the type and severity of the adverse events. All the target lesions were evaluated using multidetector computed tomography (CT) (Lightspeed Pro16, GE Healthcare Japan, Tokyo, Japan), which scans every 5 mm. The tumor measurements were performed by the physicians in charge of the respective patients in clinical practice and calculated separately for the response in the individual primary or metastatic sites. The response was assessed by multidetector CT at least every 2 cycles of treatment, according to the ResponseEvaluation Criteria in Solid Tumors, version 1.0 (RECIST).[6]

Statistical Analysis

To identify an optimal threshold for the prediction of >30% tumor reduction (partial response), receiver operating characteristics analysis was performed by incrementally increasing the cutoff values and recalculating the corresponding true-positive and false-negative rates. The relationship between the longest tumor diameter at baseline the tumor size reduction rate was assessed using the Spearmancorrelation test and the Mann-Whitney U test. Independent Student's t tests and analyses of variance were used in the univariate analysis for binomial variables, and correlation coefficient analyses were used for continuous variables. Multivariate linear regression analysis was used for the multivariate analysis. Statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0, for Windows (SPSS, Chicago, IL). Two-tailed $P < .05$ was considered significant.

RESULTS

Patient Characteristics

The clinical and pathologic characteristics of the patients treated with TKIs are listed in Table 1. The median follow-up was 12.2 months (range 3.8-29.7). Overall, 16 patients (30%) demonstrated a partial response and 26 (48%) had stable disease according to the RECIST, indicating that 78% of the patients experienced a clinical benefit from these targeted agents. Progression was observed in 9 patients (17%) and early treatment failure before the initial assessment occurred in 3 patients (5%) owing to sorafenib-induced erythema multiforme.[7]

Table 1. Patient characteristics

Characteristic	Patients (n)
Total	54 (100)
Sex	
Male	43 (80)
Female	11 (20)
Age (y)	
Median	62
Range	25-80
ECOG performance status	
0	32 (59)
1	16 (30)
2	6 (11)
Tumor histologic type	
Clear cell	43 (80)
Clear cell plus sarcomatoid components	6 (11)
Papillary	2 (6)
Chromophobe	1 (2)
Xp translocation	1 (2)
Nephrectomy	
Yes	39 (72)
No	15 (28)
Cytokine therapy	
IL-2 and IFN	11 (20)
IFN	20 (37)
None	23 (43)
Tyrosine-kinase inhibitor	
Sunitinib	33 (61)
Sorafenib	21 (39)
Baseline serum laboratory findings	
Hemoglobin (g/dL)	
Median	11.8
Range	6.2-17.7
Corrected calcium (mg/dL)	
Median	9.3
Range	8.5-10.5
Lactate dehydrogenase (U/L)	
Median	173
Range	101-550
C-reactive protein	
Median	0.77
Range	0.03-19.4

ECOG, Eastern Cooperative Oncology Group; IL-2, interleukin-2; IFN, interferon.
Data in parentheses are percentages.

Response to Individual Targeted Lesions

We investigated the objective response of the individual primary or metastatic sites. A total of 155 tumors were examined, including 16 primary kidney lesions and 92 pulmonary, 26 lymph node, 10 liver metastatic, 6 adrenal gland, and 5 soft tissue sites. The mean ± standard deviation tumor size reduction rate was 23.8% ± 56.6%, and the tumor size was reduced by >30% in 103 tumors (66.5%) and >50% in 75 tumors (48.3%).

Correlation Between Initial Tumor Size and Tumor Size Reduction of Individual Targeted Lesions

We investigated the correlation between the initial tumor size and the tumor size reduction rate of the indi-

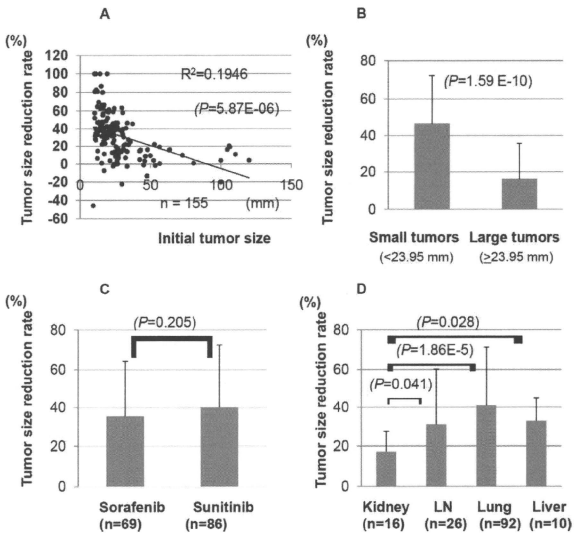

Figure 1. Association between primary tumor size and tumor size reduction. **(A)** Correlations between primary tumor size and tumor size reduction for individual tumor lesions. Smaller tumors demonstrated significant tumor size reduction compared with larger tumors. **(B)** Optimal threshold for prediction of >30% reduction (partial response) was 23.95 mm, as identified by receiver operating characteristics analysis. **(C)** No difference in tumor reduction rate demonstrated between sorafenib and sunitinib. **(D)** Primary kidney tumors demonstrated significantly small tumor size reduction compared with lymph node, metastatic lung, or liver lesions.

vidual targeted lesions. The linear association between the initial tumor size and the tumor size reduction is shown in Figure 1A. The correlation coefficient (r) was −0.441, indicating that a moderate to strong reverse association was confirmed between them ($P < .001$, Fig. 1A). Receiver operating characteristic curve analysis was performed using the clinical criteria of a partial response (>30% reduction) to separate those with and without a response. The area under the receiver operating characteristic curve was 0.814 ± 0.040, and the optimal detection threshold was 23.95 mm, with a sensitivity of 80.0% and specificity of 74.1%. When these tumors were divided into 2 groups at the threshold value (23.95 mm), the smaller tumors demonstrated a significantly greater size reduction than did the larger group ($P < .001$, Fig. 1B). In addition, among these patients, 16 had evaluable primary tumor and metastatic sites, when they were started with TKIs as induction therapy. The initial size of the 16 primary kidney tumor (77.8 ± 27.8 mm) was significantly larger than the metastatic lesions of the same patients (24.0 ± 12.7 mm, $P < .001$). Similarly, the tumor reduction rate of the primary tumor (16.1% ± 17.1%) was also significantly smaller than the metastatic lesions (43.2% ± 26.5%, $P < .001$).

Variables for Tumor Size Reduction

The relationship between the tumor reduction rate and the studied factors was investigated. The studied factors included initial tumor size, disease site, performance status, history of nephrectomy, history of cytokine therapy, TKI used (sunitinib or sorafenib), blood hemoglobin concentration, blood neutrophil count, blood thrombocyte count, serum calcium concentration, and serum lactate dehydrogenase concentration before the administration of TKIs. In the present study, no difference was found between the sorafenib-treated and sunitinib-treated lesions (Fig. 1C). In addition, the tumor reduction rate of the primary kidney was significantly smaller than that of the metastatic lymph node, pulmonary lesion, or liver lesion (Fig. 1D). However, no difference in the reduction rate was seen among the lymph node, lung metastatic, and liver metastatic lesions. On univariate analysis, the initial tumor size and the target organ were associated with the individual size reduction rate (Fig. 1A,B,D). Multivariate linear regression analysis revealed that only

the initial tumor size was also independently associated with the individual size reduction rate ($P < .001$).

COMMENT

It has long been proposed that bulky disease is an adverse prognostic factor during chemotherapy for lymphoma or solid cancer.[8,9] In contrast, the significance of bulky disease when using target therapies has not yet been made clear. For instance, many had assumed that antibody therapy would be ineffective against bulky disease; however, a Phase II study of rituximab (anti-CD20 antibody) for bulky (>10 cm) low-grade lymphoma showed that standard rituximab therapy resulted in a good response rate (43%). In addition, however, they showed that the serum antibody concentration correlated negatively with the baseline tumor bulk.[10] Antiangiogenesis therapy had also been assumed to be ineffective against bulky disease, but this has not been clinically proved. We have demonstrated for the first time that the initial tumor size correlated negatively with the tumor reduction rate in targeted therapy for mRCC.

Up-front cytoreductive nephrectomy, followed by systemic therapy, been established as the standard of care for mRCC in the cytokine era.[1,2] Even for the patients with high-risk and locally advanced RCC, neither preoperative nor postoperative medical treatment has been recommended because of the real lack of effective systemic therapiespreviously available. Therefore, the treatment strategy for RCC must be reconsidered in this targeted therapy era.

According to our results, large tumors will seldom become smaller when TKIs are administered. Therefore, it might be infrequent that an unresectable tumor would become resectable, although no objective criteria exist to define surgical resectability. We believe that the greatest benefit of preoperative approaches in the setting of mRCC is that they can as a litmus test to reserve cytoreductive nephrectomy for only those whowill benefit from the procedure.

Possibly, the resolution of CT scans could affect the tumor size reduction rate. Small lesions might appear to shrink more owing to slice variation and not true size changes. However, we used multidetector CT, which scans every 5 mm. The minimal initial tumor size was 10 mm in the present study, because we excluded tumors that were <10 mm in diameter. Therefore, we believe that the potential issues regarding the resolution of the CT scans did not have a major effect on our conclusions. In addition, when micrometastasis is considered to be of a very small size, adjuvant therapy after radical nephrectomy could meet our expectation of reduced recurrence. Sorafenib and sunitinib have been the focus of adjuvant therapy for patients with resected primary tumors with a high risk of recurrence. Three randomized trials are comparing these agents to placebo in the adjuvant setting: Sunitinib Treatment in Renal Adjuvant Cancer (S-TRAC), Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE), and Sorafenib With Placebo in Patients With Resected Primary Renal Cell (SORCE).[11]

Very recently, a study similar to ours was published by Han et al.[12] In their study, the initial tumor enhancement on contrast-enhanced CT could be useful as a clinical predictor during targeted therapy, because it was associated with tumor size reduction of the individual metastases in patients with mRCC who had received targeted therapy.[12] Because of the antiangiogenic therapy, their rationale was quite reasonable. Tumor enhancement was associated not only with tumor size reduction, but also with progression-free survival of the treated patients. However, compared with their study, our study was simpler and could be performed without contrast medium, which can be detrimental to patients with a solitary kidney. In addition, it can be adapted for patients with renal dysfunction, as well as patients who are allergic to contrast medium.

In addition to the treatment paradigm of RCC, our results suggest a weakness in the RECIST, currently the most commonly used system to determine the response in clinical trials and clinical practice. In our study, the longest diameter of large tumor demonstrated a relatively smaller reduction rate than thatof the metastatic small tumor. Therefore, large primary tumors will have an important effect on the overall objective when these are included in the RECIST measurements.Therefore, whether the target lesion includes the large primary and/or metastatic lesions should be considered in calculating the overall response according to the RECIST.

CONCLUSIONS

The initial tumor size was inversely associated with the tumor reduction rate of the individual metastatic sites and primary tumors in patients with mRCC who underwent targeted therapy. Although our small study was preliminary and additional investigations are necessary, we believe that this simple observation might be useful for physicians who treat patients with mRCC, as exemplified by the consideration of the pre- and postoperative approaches. In addition, in assessing clinical trials of targeted agents for metastatic RCC using the RECIST, we might need to consider this association.

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CASE REPORT

A case study of metastatic Xp11.2 translocation renal cell carcinoma effectively treated with sunitinib

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Abstract We report a case of Xp11.2 translocation renal cell carcinoma (RCC) whose lung metastases were effectively treated with sunitinib. A 43-year-old woman presenting with upper abdominal pain was diagnosed with a left renal tumor. Laparoscopic left radical nephrectomy was performed. Histopathological examination of the surgical specimen revealed a clear-cell carcinoma of the left kidney. Two years later, multiple lung metastases were detected and the patient was treated daily with 50 mg sunitinib. A computed tomography scan performed after 2 cycles of sunitinib treatment revealed partial regression of these metastases. The partial regression has been maintained for >3 years. In retrospective evaluation of the primary RCC, tumor cells showed strong nuclear staining for transcription factor E3 (TFE3) protein and *TFE3* split-fluorescence in-situ hybridization revealed translocation involving the *TFE3* gene. These findings strongly support diagnosis of Xp11.2 translocation RCC.

Keywords Renal cell carcinoma · Xp11.2 translocation · Sunitinib · Fluorescence in situ hybridization

Introduction

Xp11.2 translocation renal cell carcinoma (RCC) is reported to be common in children and believed to be extremely rare in adults. Argani et al. [1] reported 28 adult cases of Xp11.2 translocation RCC with strong female predominance (female to male ratio, 22:6) and a tendency to spread to perirenal lymph nodes. However, little is known about the natural behavior of this tumor, and treatment strategies have not yet been established. This subset of RCC is characterized by various translocations involving chromosome Xp11.2 that result in gene fusion involving the *transcription factor binding E3* (*TFE3*) gene. In a large randomized study, administration of sunitinib, an orally active multikinase inhibitor, resulted in significant prolongation of progression-free survival (PFS) of patients with clear-cell histology of RCC [2]. However, evidence for its efficacy in non-clear-cell histology, especially Xp11.2 translocation RCC, is lacking. We report the case of a patient with metastatic Xp11.2 translocation RCC who achieved an excellent therapeutic response to sunitinib treatment. We further discuss the mechanisms of therapeutic response to sunitinib treatment.

Case report

A 43-year-old woman who presented with sudden onset of upper abdominal pain is the subject of this study. Ultrasonography and computed tomography (CT) revealed a left renal mass measuring 10 cm in diameter with a tumor thrombus in the left renal vein (Fig. 1). She was diagnosed with RCC of clinical stage T3bN0M0, and laparoscopic radical nephrectomy was performed without complications. Her perioperative period was uneventful. Histopathological examination of the surgical specimen revealed a clear-cell carcinoma (Fig. 2), G2 > G3, INF alpha, and pT3bpN0 with a negative surgical margin. The patient developed multiple lung metastases (maximum diameter 1.0 cm)

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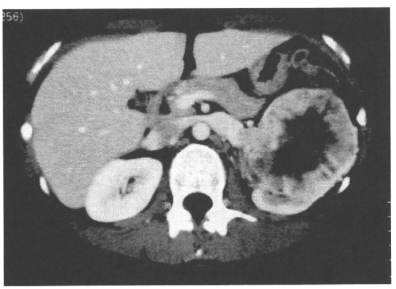

Fig. 1 Computed tomography reveals a left renal mass measuring 10 cm in diameter with a tumor thrombus localized in the left renal vein

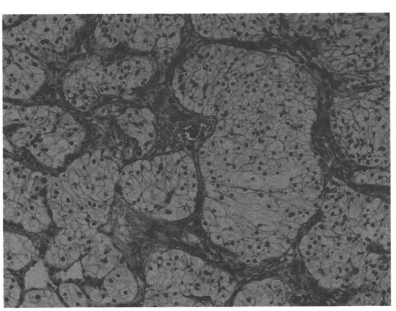

Fig. 2 H&E staining of the surgical specimen (×200)

2 years after the nephrectomy (Fig. 3a) and was administered 50 mg sunitinib daily. A CT scan performed 6 weeks after the initiation of treatment confirmed the partial regression of the lung metastases (Fig. 3b). Forty-two months after initiation of the sunitinib treatment, the partial regression has been maintained (Fig. 3c). Dose reduction to 37.5 mg/day was required in subsequent cycles because of fatigue, and the patient is being treated with the same sunitinib dosage without major adverse effects.

We performed a retrospective evaluation of the primary RCC tumor because of the differential diagnosis of Xp11.2 translocation RCC that was added to the new World Health Organization classification in 2004. The tumor cells showed strong nuclear staining for TFE3 protein (Fig. 4) and were positive for *TFE3* split-fluorescence in-situ hybridization (FISH: Fig. 5). Consequently, this case was diagnosed as Xp11.2 translocation RCC.

Discussion

Xp11.2 translocation RCC, which was originally reported to have papillary architecture and clear cytoplasm, is often confused with clear-cell or papillary RCC, probably because appropriate diagnostic methods are not performed to confirm the diagnosis. In recent years, various forms of Xp11.2 translocation RCC have been identified and characterized at the morphological and molecular levels [3]. Such translocations result in gene fusion between the *TFE3* gene located on chromosome Xp11.2 and various partner genes. Argani et al. [1] reported that nuclear immunoreactivity for TFE3 protein is a highly sensitive and specific assay for neoplasm bearing *TFE3* gene fusion. The antibody used for this procedure recognizes the C-terminal portion of the protein, which is retained in all TFE3 fusion proteins. The native TFE3 protein is known to be expressed ubiquitously but is undetectable in normal tissues by immunohistochemical analysis. It is believed that different *TFE3* gene fusion consistently lead to overexpression of the protein [1]. However, some authors have pointed out that the TFE3 antibody is only moderately reliable [4]. A FISH assay performed on formalin-fixed, paraffin-embedded tissue is known to be more sensitive in detecting the Xp11.2 translocation [5]. We established the *TFE3* split-FISH assay by utilizing the FISH probes located on both sides of the *TFE3* gene (GSP Research Institute, Kawasaki, Japan). The 5′-fragment and 3′-fragment of the *TFE3* gene were labeled with Texas Red™ and fluorescein isothiocyanate, respectively. Tumor cells with the translocation have a split signal (red and green signals are observed separately), whereas cells without the translocation have a fused signal (Fig. 5). In this case, although karyotype analysis was not performed, the expression of TFE3 protein was confirmed immunohistochemically and the *TFE3* split-FISH analysis showed the translocation involving the *TFE3* gene. This is the first case of Xp11.2 translocation RCC confirmed by the *TFE3* split-FISH assay and also effectively treated with sunitinib.

The TFE3 fusion proteins are believed to bind to the *MET* promoter region, leading to its activation [6]. Up-regulation of *MET* by TFE3 fusion proteins results in strong *MET* autophosphorylation and activation of downstream signaling in the presence of HGF. Tyrosine kinase inhibitors, for example sunitinib, have changed treatment strategies for management of metastatic RCC. However, the activity of sunitinib in non-clear-cell histology has not been fully evaluated. Malouf et al. [7] reported the efficacy of molecule-targeted therapy for Xp11.2 translocation RCC. Twelve Xp11.2 translocation RCC patients with metastases had received targeted therapy (eleven patients received sunitinib, one received mammalian-targeted rapamycin inhibitor), and comparison with cytokine therapy

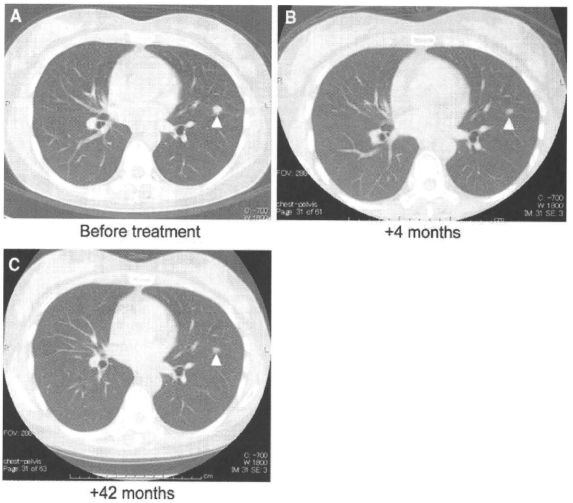

Fig. 3 Computed tomography reveals lung metastasis (*arrow*) before administration of sunitinib (**a**), 4 months after the initiation of sunitinib (**b**), and 42 months after the initiation of sunitinib (**c**)

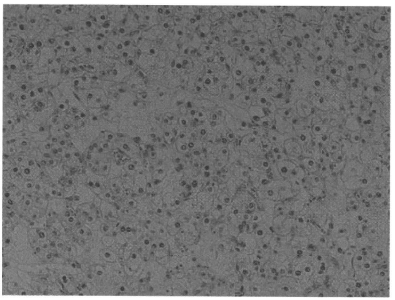

Fig. 4 Immunohistochemical evaluation revealed tumor cells showing nuclear-specific staining for TFE3 protein

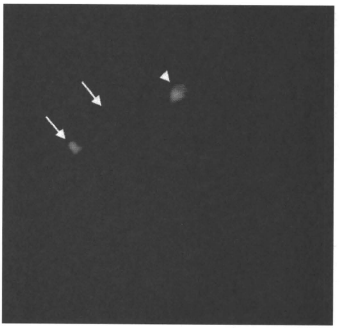

Fig. 5 Split-fluorescence in-situ hybridization of Xp11.2 translocation renal cell carcinoma. *Arrows* indicate the translocated Xp11.2 fragments, and the *arrowhead* indicates the normal X chromosome

revealed favorable response rate and PFS. However, in their study, diagnosis for most of the patients of Xp11.2 translocation was confirmed by immunohistochemical analysis, and only two were diagnosed cytogenetically. Because immunohistochemical diagnosis of TFE3 protein expression is sometimes difficult and ambiguous, it may be better to define the presence of the Xp11.2 translocation both genetically and immunohistochemically. With such clear distinction, comparison of the clinical characteristics of RCC with Xp11.2 translocation can be achieved.

Possible mechanisms explaining the effect of sunitinib on Xp11.2 translocation RCC tumors include RTK inhibition and direct anti-tumor and anti-angiogenic activity by targeting VEGF, PDGFR, and RET receptors [8–10]. Stacchiotti et al. [11] reported that the anti-tumor activity of sunitinib in alveolar soft part sarcoma, which is also associated with Xp11.2 translocation, may be mediated mainly by PDGFRs. However, results from another study

of MET suggests that in addition to up-regulated TFE3 fusion protein expression, as shown by preclinical assays [12], activation of RET may also occasionally occur after activation of MET by the HGF ligand. Currently, no data are available on the activity of sunitinib on MET. However, SU5416, another RTK inhibitor, that is chemically related to sunitinib and has similar functional groups, inhibits the activation of HGF/MET in hepatocellular carcinoma. This suggests that sunitinib might be involved in the HGF/MET down-signaling switch off [13].

This case study illustrates the efficacy of sunitinib in metastatic RCC associated with Xp11.2 translocation. However, further studies are required to confirm the clinical benefits of RTK inhibitors in patients with this type of RCC.

Conflict of interest No author has any conflict of interest.

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Original Article

Overall Survival and Updated Results from a Phase II Study of Sunitinib in Japanese Patients with Metastatic Renal Cell Carcinoma

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Background: In a phase II, open-label, multicentre Japanese study, sunitinib demonstrated antitumour activity and acceptable tolerability in metastatic renal cell carcinoma patients. Final survival analyses and updated results are reported.

Methods: Fifty-one Japanese patients with a clear-cell component of metastatic renal cell carcinoma (25 treatment-naïve; 26 cytokine-refractory) received sunitinib 50 mg orally, once daily (Schedule 4/2). Overall and progression-free survivals were estimated by the Kaplan–Meier method. Objective response rate (per Response Evaluation Criteria in Solid Tumours) and safety were assessed with an updated follow-up.

Results: First-line and pretreated patients received a median 6.0 and 9.5 treatment cycles, respectively. Investigator-assessed, end-of-study objective response rate was 52.0, 53.8 and 52.9% in first-line, pretreated and overall intent-to-treat populations, respectively. The median progression-free survival was 12.2 and 10.6 months in first-line and pretreated patients, respectively. Fourteen patients per group died (56 and 54%), and the median overall survival was 33.1 and 32.5 months, respectively. The most common treatment-related Grade 3 or 4 adverse events and laboratory abnormalities were fatigue (24%), hand-foot syndrome (18%), decreased platelet count (55%), decreased neutrophil count (53%) and increased lipase (49%). No Grade 5 treatment-related adverse events occurred. Forty patients (78%) required dose reduction, and 13 (25%) discontinued, due to treatment-related adverse events.

Conclusions: With the median overall survival benefit exceeding 2.5 years, and acceptable tolerability, in first-line and pretreated Japanese metastatic renal cell carcinoma patients with Eastern Cooperative Oncology Group performance status 0/1, sunitinib showed a favourable risk/benefit profile, similar to Western studies. However, there was a trend towards greater efficacy and more haematological adverse events in Japanese patients.

Key words: Japanese – phase II – renal cell carcinoma – sunitinib

INTRODUCTION

Sunitinib is an orally administered, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3 and platelet-derived growth factor (PDGF) receptors α and β (1). Data from Western studies of patients with treatment-naïve and cytokine-pretreated renal cell carcinoma (RCC) have demonstrated consistent benefit with single-agent sunitinib therapy, with investigator-assessed objective response rates (ORRs) of up to 47 and 49% and median overall survival (OS) times of 26.4 and 23.9 months, for first- and second-line treatment, respectively (2–5).

We previously reported interim results of the first Japanese phase II study of single-agent sunitinib in 51 patients with metastatic RCC, demonstrating comparable efficacy and tolerability to that observed in Western patients (6). In this study, the primary endpoint of ORR, based on independent review, was 48.0% in treatment-naïve patients, 46.2% among pretreated patients and 47.1% in the overall intent-to-treat (ITT) population. Median progression-free survival (PFS) was 46.0, 33.6 and 46.0 weeks (10.6, 7.8 and 10.6 months) in the same patient groups, respectively. As a result of these findings, multinational approvals of sunitinib for treatment of first- and second-line advanced RCC now include approval in Japan for patients with RCC not indicated for curative resection and patients with metastatic RCC.

Although the primary endpoint of the Japanese phase II study was met at the time of interim analysis, the median OS had not yet been reached. Here we report the final OS analysis, as well as updated efficacy and safety findings.

METHODS

Patients

Patients with histologically proven RCC with a clear-cell component and metastases were included in the study. No prior systemic therapy was permitted in the first-line population, and previous treatment with only one cytokine-based regimen (that could include multiple cytokines) was permitted in the pretreated group. Additional eligibility and exclusion criteria [e.g. all patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1] have been reported previously (6).

Study Design and Treatment

This was a multicentre, open-label, non-randomized, single-arm, phase II study of sunitinib (SUTENT®; Pfizer, New York, NY, USA) in patients with treatment-naïve or cytokine-pretreated metastatic RCC. The study was carried out in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and was approved by the institutional review board at each participating centre. All patients provided written informed consent.

Sunitinib was administered orally at a starting dose of 50 mg once daily in the morning, without regard to meals. Treatment was given in repeated 6-week cycles consisting of 4 weeks on therapy, followed by 2 weeks off (Schedule 4/2). Intrapatient dose reductions or interruptions were permitted to manage adverse events (AEs), according to the protocol. Treatment was continued until disease progression, requirement for additional anticancer therapy, development of left ventricular systolic dysfunction or withdrawal of consent.

Assessments

The primary endpoint was ORR in the ITT population based on independent review, and secondary endpoints included the investigator-assessed ORR, duration of response, time to tumour response, PFS, OS and safety. Tumour assessments were based on the Response Evaluation Criteria in Solid Tumours (RECIST) (7), with computed tomography or MRI scans (with or without X-rays) obtained every 6 weeks by investigators. Safety and tolerability were monitored as previously described (6), and AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). A post-study survival survey was conducted once per year and included all patients who received at least one dose of sunitinib.

Statistical Methods

In the primary efficacy analysis of the ITT population, the ORR and 95% confidence intervals (CIs) were calculated based on independent review, with the same analysis performed for investigators' assessments. Sample sizes of 26 and 25 patients were required for the pretreated and first-line populations, respectively, to provide a power of 80% with an alpha level of 2.5%. These sample size calculations were based on the threshold values for response rates (5% for pretreated patients and 10% for the first-line population) considered to be clinically ineffective for each population. The efficacy of sunitinib would be confirmed if the lower limit of the 95% CI of the observed ORR was greater than or equal to the threshold rate for each population. Time-to-event endpoints were estimated using the Kaplan–Meier method (8).

Independent review of imaging scans was discontinued after the interim analysis in February 2007 when the primary endpoint was met; therefore, only updated investigator-assessed results are reported herein.

RESULTS

Patient Characteristics and Disposition

A total of 51 patients were enrolled at 12 study centres in Japan. The first-line population consisted of 25 patients with a mean age of 56.6 years (range, 33–76), and the pretreated

population comprised 26 patients with a mean age of 61.1 years (range, 34–77). At baseline, the ECOG PS of all patients was 0 or 1, and the lung was the most prevalent site of metastases. Additional patient baseline characteristics have been described previously (6).

All 51 patients received at least one dose of sunitinib. At the time of analysis, the first-line and pretreated groups received a median 6.0 and 9.5 treatment cycles, respectively. No patients continued to receive sunitinib after disease progression in the first-line group; however, 9/18 patients (50%) with progressive disease in the pretreated group continued to receive sunitinib after progression because of continuing benefit. Ten patients (20%) had completed the study (6 patients in the first-line group and 4 patients in the pretreated group) and 41 (80%) had discontinued (19 and 22 patients, respectively). Reasons for discontinuation included disease progression (13 patients in each group) and treatment-related AEs (6 and 7 patients, respectively, including 1 pretreated patient with a laboratory abnormality); in addition, within the pretreated group, 1 patient died and 1 patient had discontinued due to AEs unrelated to treatment.

Efficacy

At the end of the study, the investigator-assessed ORR (95% CI) was 52.0% (31.3, 72.2) in the first-line population, 53.8% (33.4, 73.4) in the pretreated population and 52.9% (38.5, 67.1) in the overall ITT population (Table 1). An additional 13 patients (6 in the first-line population and 7 in the pretreated group) had a best response of stable disease $\geq$6 weeks. The median time to tumour response was 10.0 and 10.5 weeks, and the duration of response was 25.8 and 8.8 months in the first-line and pretreated groups, respectively.

Median PFS was 12.2 months (95% CI: 7.8, 48.8) in the first-line population and 10.6 months (95% CI: 6.6, 24.2) in the pretreated population (Figure 1). A total of 14 patients in each arm died (56 and 54%, respectively), and the median OS was 33.1 months (95% CI: 14.8, not reached) and 32.5 months (95% CI: 19.8 months, not reached) for the first-line and pretreated groups, respectively (Figure 2).

Safety

The most frequently reported treatment-related AEs of all grades were anorexia (72%), and skin discolouration and diarrhoea (both 64%) in the first-line population (Table 2), and skin discolouration and fatigue (both 81%), as well as anorexia and hypertension (both 65%) in the pretreated population (Table 3). In all patients, the majority of AEs were mild to moderate (Grades 1 or 2) in severity. Commonly reported Grade 3, treatment-related AEs in the first-line and pretreated groups, respectively, included diarrhoea (16 and 15%), fatigue (16 and 27%), hand-foot syndrome (16 and 19%) and hypertension (12 and 19%). A total of three Grade 4, treatment-related AEs were reported overall (hypomagnesaemia, dyspnoea and fatigue; all $n = 1$), and no Grade 5 events occurred.

Table 1. Best RECIST-defined tumour response at study end (investigator assessment)

Response	First-line population ($n = 25$)	Pretreated population ($n = 26$)	Total population ($n = 51$)
Objective response rate, %	52.0%	53.8%	52.9%
(95% CI)	(31.3, 72.2)	(33.4, 73.4)	(38.5, 67.1)
Partial response, *n*	13	14	27
Stable disease $\geq$ 6 weeks, *n*	6	7	13

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumours.

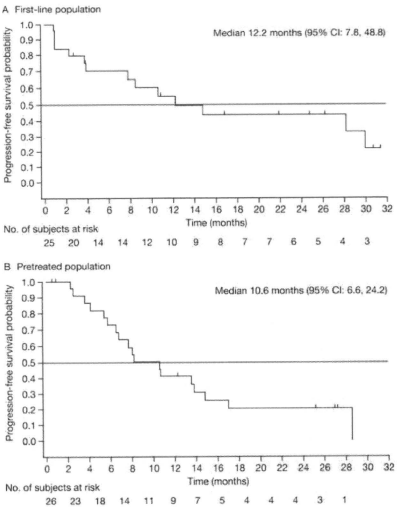

Figure 1. Kaplan–Meier estimates of progression-free survival in the (A) first-line and (B) pretreated patient populations. CI, confidence interval.

Laboratory abnormalities were frequently reported in both patient populations (Tables 2 and 3). The most common abnormalities were decreased counts for platelets (96%), white blood cells (88%), lymphocytes (84%) and neutrophils (76%) in the first-line population (Table 2) and decreased counts for platelets (88%), white blood cells (85%) and neutrophils (85%) and increased lipase (77%) in the pretreated population (Table 3). Grade 3 or 4 laboratory abnormalities

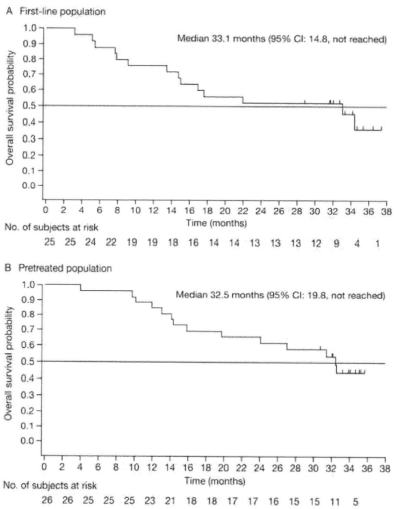

Figure 2. Kaplan–Meier estimates of overall survival in the (A) first-line and (B) pretreated patient populations. CI, confidence interval.

reported in at least 50% of patients in the first-line and pretreated populations, respectively, included decreased counts for platelets (56 and 54%) and neutrophils (44 and 62%) and increased lipase (32 and 65%). Decreased lymphocyte count and increased lipase were the most frequently reported Grade 4 laboratory abnormalities in the first-line population (each $n = 3$; 12%), while increased lipase was the most common Grade 4 abnormality in the pretreated population ($n = 5$; 20%). No Grade 5 laboratory abnormalities were observed.

The overall incidences of QT-corrected interval prolongation ($n = 2$; 1 patient each with Grades 1 and 2 severity) and decreased left ventricular ejection fraction (LVEF; $n = 2$; 1 patient each with Grades 2 and 3 severity) were low (both 4%) with neither condition existent at baseline. Both cases of QT-corrected interval prolongation were not clinically significant and resolved without treatment changes. One case of decreased LVEF was reported as a serious AE and resolved following treatment discontinuation.

Treatment-related AEs led to dose modifications (dose reduction or temporary discontinuation) in a total of 46 patients (90%), comprising 22 and 24 patients in the first-line and pretreated populations, respectively. Overall, the most frequent AEs leading to treatment changes were decreased counts for platelets ($n = 26$; 51%), neutrophils ($n = 23$; 45%) and white blood cells ($n = 15$; 29%), as well as fatigue ($n = 13$; 26%) and hand-foot syndrome ($n = 11$; 22%). The majority of these events resolved, either with or without standard treatment, and did not result in sunitinib discontinuation. Discontinuation due to treatment-related AEs occurred among 13 patients (25%), and the most common AEs involved were fatigue, decreased LVEF and hypertension.

DISCUSSION

In this phase II, open-label, multicentre study of sunitinib 50 mg/day (Schedule 4/2) in Japanese patients with first-line and cytokine-refractory metastatic RCC, sunitinib showed significant antitumour activity, including a median OS benefit exceeding 2.5 years, and was generally well tolerated. The primary endpoint of ORR was met at the first interim analysis (February 2007 data cutoff) (6), and increased in each patient population as the study continued to produce a final ORR of 52.9% in all patients, 52.0% in the first-line population and 53.8% in the pretreated population.

Final results for the median PFS (12.2 and 10.6 months for first-line and pretreated patients, respectively) and the median OS (33.1 and 32.5 months, respectively) indicate that sunitinib provides substantial survival benefits in both treatment-naïve and cytokine-pretreated Japanese patients with metastatic RCC. Notably, the results cannot answer whether sunitinib should be used in treatment-naïve or cytokine-pretreated patients, since there may be possible differences in clinical backgrounds of each population.

Although cross-study comparisons should be interpreted with care due to methodological issues, both the median PFS and OS were longer in this study, compared with sunitinib trials in Western patients with metastatic RCC. In a recent phase III trial of first-line therapy, the median PFS was 11 months and the median OS was 26.4 months in Western patients (5) (compared with 12.2 and 33.1 months, respectively, in the present study), while, in two consecutive phase II trials of second-line therapy, the median PFS was 8.7–8.8 months with the median OS of 23.9 months in the latter trial (3,4) (compared with 10.6 and 32.5 months, respectively, in the present study). Similarly, investigator-assessed ORRs were ~5% higher in Japanese patients in this trial compared with Western patients (2–5). Preliminary findings from an ongoing, expanded-access trial of sunitinib in patients with metastatic RCC found that efficacy was comparable between patients in Asia-Pacific and Western countries (9). However, the expanded access trial included both treatment-naïve and pretreated patients, as well as patients from a greater geographical range than the present study, which may have affected the outcome. Finally, the >50% ORR reported in our study also compares favourably with the ORR of 14.7% reported in a phase II study of sorafenib in Japanese patients with unresectable RCC (10).

Safety findings from the present study as well as the ongoing expanded access trial (9) indicate that the safety profile of sunitinib is generally similar in Asian and

Table 2. Treatment-related adverse events and laboratory abnormalities reported in at least 25% of patients in the first-line population

	Maximum NCI CTCAE[a] grade[b] ($n = 25$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Adverse event, *n* (%)					
Anorexia	5 (20)	10 (40)	3 (12)	0	18 (72)
Skin discolouration	15 (60)	1 (4)	0	0	16 (64)
Diarrhoea	8 (32)	4 (16)	4 (16)	0	16 (64)
Pyrexia	9 (36)	6 (24)	0	0	15 (60)
Nausea	6 (24)	7 (28)	2 (8)	0	15 (60)
Stomatitis	8 (32)	5 (20)	1 (4)	0	14 (56)
Hypertension	2 (8)	9 (36)	3 (12)	0	14 (56)
Dysgeusia	4 (16)	9 (36)	0	0	13 (52)
Hand-foot syndrome	2 (8)	7 (28)	4 (16)	0	13 (52)
Rash	10 (40)	2 (8)	0	0	12 (48)
Fatigue	2 (8)	6 (24)	4 (16)	0	12 (48)
Malaise	7 (28)	1 (4)	1 (4)	0	9 (36)
Face oedema	6 (24)	3 (12)	0	0	9 (36)
Vomiting	3 (12)	4 (16)	2 (8)	0	9 (36)
Oedema peripheral	6 (24)	2 (8)	0	0	8 (32)
Laboratory abnormality, *n* (%)					
Decreased platelet count	7 (28)	3 (12)	12 (48)	2 (8)	24 (96)
Decreased white blood cell count	2 (8)	14 (56)	5 (20)	1 (4)	22 (88)
Decreased lymphocyte count	1 (4)	10 (40)	7 (28)	3 (12)	21 (84)
Decreased neutrophil count	2 (8)	6 (24)	9 (36)	2 (8)	19 (76)
Increased lactate dehydrogenase	11 (44)	5 (20)	1 (4)	0	17 (68)
Increased lipase	5 (20)	3 (12)	5 (20)	3 (12)	16 (64)
Increased aspartate aminotransferase	10 (40)	2 (8)	2 (8)	1 (4)	15 (60)
Increased creatinine	7 (28)	6 (24)	2 (8)	0	15 (60)
Increased alanine aminotransferase	7 (28)	3 (12)	3 (12)	0	13 (52)
Decreased haemoglobin	6 (24)	5 (20)	1 (4)	0	12 (48)
Increased amylase	6 (24)	3 (12)	2 (8)	0	11 (44)
Increased alkaline phosphatase	6 (24)	3 (12)	1 (4)	0	10 (40)
Increased bilirubin	4 (16)	3 (12)	1 (4)	0	8 (32)
Decreased phosphorus	1 (4)	1 (4)	6 (24)	0	8 (32)
Decreased calcium	5 (20)	2 (8)	0	0	7 (28)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[b]No Grade 5 adverse events or laboratory abnormalities were reported.

non-Asian patients. The majority of treatment-related AEs observed in this study were Grades 1 or 2 in severity, were manageable with prespecified dose changes or standard medical treatment and did not lead to study withdrawal. The previously published analysis from this study found that patients experienced modest declines in the health-related quality of life during sunitinib treatment periods, followed by recovery during subsequent off-treatment periods (6). In combination with the AE data reported here, these results indicate that sunitinib therapy was well tolerated overall. The most frequently reported Grade 3, treatment-related AEs and laboratory abnormalities in the first-line group were diarrhoea, fatigue and hand-foot syndrome and decreased counts for platelets, neutrophils and lymphocytes, and, in the pretreated group, fatigue, hand-foot syndrome and hypertension and decreased counts for neutrophils and platelets and

Table 3. Treatment-related adverse events and laboratory abnormalities reported in at least 25% of patients in the pretreated population

	Maximum NCI CTCAE[a] grade[b] ($n = 26$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Adverse event, *n* (%)					
Skin discolouration	20 (77)	1 (4)	0	0	21 (81)
Fatigue	9 (35)	4 (15)	7 (27)	1 (4)	21 (81)
Anorexia	8 (31)	6 (23)	3 (12)	0	17 (65)
Hypertension	1 (4)	11 (42)	5 (19)	0	17 (65)
Dysgeusia	11 (42)	4 (15)	0	0	15 (58)
Rash	13 (50)	2 (8)	0	0	15 (58)
Face oedema	13 (50)	0	1 (4)	0	14 (54)
Diarrhoea	10 (38)	0	4 (15)	0	14 (54)
Hand-foot syndrome	3 (12)	6 (23)	5 (19)	0	14 (54)
Oedema peripheral	12 (46)	0	1 (4)	0	13 (50)
Epistaxis	11 (42)	0	0	0	11 (42)
Stomatitis	6 (23)	4 (15)	1 (4)	0	11 (42)
Pyrexia	4 (15)	6 (23)	1 (4)	0	11 (42)
Nausea	3 (12)	7 (27)	1 (4)	0	11 (42)
Malaise	4 (15)	3 (12)	3 (12)	0	10 (38)
Eyelid oedema	7 (27)	2 (8)	0	0	9 (35)
Dyspepsia	6 (23)	2 (8)	0	0	8 (31)
Cheilitis	5 (19)	3 (12)	0	0	8 (31)
Pain in extremity	2 (8)	2 (8)	3 (12)	0	7 (27)
Headache	6 (23)	1 (4)	0	0	7 (27)
Laboratory abnormality, *n* (%)					
Decreased platelet count	4 (15)	5 (19)	12 (46)	2 (8)	23 (88)
Decreased white blood cell count	3 (12)	15 (58)	4 (15)	0	22 (85)
Decreased neutrophil count	2 (8)	4 (15)	14 (54)	2 (8)	22 (85)
Increased lipase	0	3 (12)	12 (46)	5 (19)	20 (77)
Increased lactate dehydrogenase	16 (62)	3 (12)	0	0	19 (73)
Increased aspartate aminotransferase	13 (50)	4 (15)	2 (8)	0	19 (73)
Increased amylase	6 (23)	5 (19)	4 (15)	0	15 (58)
Decreased lymphocyte count	3 (12)	5 (19)	5 (19)	2 (8)	15 (58)
Increased alanine aminotransferase	9 (35)	4 (15)	0	0	13 (50)
Increased creatinine	6 (23)	6 (23)	1 (4)	0	13 (50)
Decreased haemoglobin	5 (19)	4 (15)	3 (12)	0	12 (46)
Decreased albumin	4 (15)	4 (15)	1 (4)	0	9 (35)
Increased alkaline phosphatase	5 (19)	3 (12)	0	0	8 (31)
Increased bilirubin	3 (12)	5 (19)	0	0	8 (31)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[b]No Grade 5 adverse events or laboratory abnormalities were reported.

increased lipase. In the preliminary report by Lee et al. (9), Asian patients treated at Asian sites had a higher frequency of leukopenia, thrombocytopenia, stomatitis and hand-foot syndrome and a lower incidence of diarrhoea, compared with non-Asian patients. Our findings are generally comparable, although the incidence of diarrhoea in our study was similar to or higher than that previously reported for Western patients (3–5), and the frequency of Grade 3 or 4

thrombocytopenia was ~25% higher among Japanese patients in our study versus the Asian patients treated at Asian sites in the expanded access trial (9). Grade 3 and 4 decreases in counts for neutrophils and platelets were also considerably more common in Japanese patients in the present study than in Western patients in prior studies.

At the current time, it is not clear why the tolerability and efficacy of sunitinib may differ to some extent in Japanese and Western populations. Analysis of sunitinib pharmacokinetic parameters from 13 Western studies and one Japanese study showed similar plasma exposure for sunitinib and its active metabolite SU12662 between the two populations (11), and we have previously reported a lack of correlation between sunitinib and SU12662 systemic exposure and body weight in Japanese and Caucasian subjects in an analysis that included pharmacokinetic data from the present study (6). Further studies are needed to validate and investigate the basis of potential sunitinib tolerability and efficacy differences in these populations. In this respect, analysis of mature data from Asian and non-Asian patients in the sunitinib expanded access trial will be of interest although, there are inherent limitations to using data from such trials.

In conclusion, sunitinib 50 mg/day on Schedule 4/2 has a favourable risk/benefit profile in Japanese patients with metastatic RCC. The median OS benefit exceeded 2.5 years in both first-line and pretreated patients, in whom ECOG PS was 0 or 1, and was accompanied by acceptable tolerability. Overall, the safety and efficacy of sunitinib was similar to that reported in Western studies, although there was a trend towards greater efficacy and an increased incidence of haematological AEs in Japanese patients.

AUTHORS' ROLES

All authors discussed the results and commented on the manuscript. Specifically, each author contributed to the study and manuscript as follows: Y.T. designed this study, conducted patient treatment and wrote/edited the manuscript; N.S. designed this study, conducted patient treatment and edited the manuscript; T.Y. designed this study, conducted patient treatment and edited the manuscript; H.F. designed this study, conducted patient treatment and edited the manuscript; M.N. designed this study, conducted patient treatment and edited the manuscript; S.M. designed this study, conducted patient treatment and edited the manuscript; T.M. designed this study and edited the manuscript; H.U. designed this study, conducted patient treatment and edited the manuscript; N.N. designed this study, conducted patient treatment and edited the manuscript; M.T. designed this study, conducted patient treatment and edited the manuscript; Y.H. designed this study, conducted patient treatment and edited the manuscript; N.A. analysed the data and wrote/edited the manuscript; B.H. analysed the data and edited the manuscript; S.N. designed this study, conducted patient treatment and edited the manuscript; and H.A. designed this study, conducted patient treatment, edited the manuscript and serves as the corresponding author for this paper.

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Conflict of interest statement

The authors, Naoki Agata and Brett Houk, are employees of Pfizer Inc.

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Relationship Between Bone Mineral Density and Androgen-deprivation Therapy in Japanese Prostate Cancer Patients

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OBJECTIVES To examine Japanese patients who had received androgen-deprivation therapy (ADT) for longer periods, as it is known that ADT of patients with prostate cancer reduces their bone mineral density (BMD). However, our previous cross-sectional study revealed that short-term ADT (average, 23.5 months) does not significantly increase the prevalence of osteoporosis in Japanese patients.

METHODS The subjects consisted of 201 native Japanese patients with prostate cancer. They comprised 113 ADT-treated and 88 hormone-naive patients. Lumbar spine, total hip, and femoral neck BMDs were measured by dual-energy x-ray absorptiometry and expressed in standard deviation units relative to the scores of young adult men (*T*-score) or age-matched men (*Z*-score). Serum levels of bone metabolism markers were also measured.

RESULTS The ADT-treated patients had significantly lower BMD values, *T*-scores, and even *Z*-scores than the hormone-naive patients ($P < .001$). For patients who were hormone-naive, ADT-treated for less than 2 years, and ADT-treated for more than 2 years, the osteoporosis prevalence was 4.5% (4/88), 12.1% (4/33), and 10.8% (4/37), respectively. The ADT-treated patients had significantly higher serum amino-terminal telopeptide levels than the hormone-naive patients ($P = .014$), but significantly lower serum carboxy-terminal telopeptide of type-I collagen levels than the ADT-treated patients with bone metastasis ($P < .001$).

CONCLUSIONS Our cross-sectional study confirmed that both ADT-treated and hormone-naive Japanese patients with prostate cancer have low rates of osteoporosis. These findings are different from those of studies in western countries. Genetic and hormonal or other environmental factors may result in population differences in the characteristics of prostate cancer and BMD. UROLOGY 75: 1131–1137, 2010. © 2010 Elsevier Inc.

Cancer treatment-induced bone loss is one of the complications associated with androgen-deprivation therapy (ADT) of patients with prostate cancer. It is of particular concern because it can lead to osteoporosis and bone fractures, which not only negatively impact patient quality of life but also overall survival.[1-3] However, these studies were performed in western countries. This is of relevance because several studies, including a breast cancer study of patients treated with aromatase inhibitor, revealed that Caucasian and Japanese women show racial differences in bone mineral density (BMD) and the incidence of bone fracture.[4-6] Moreover, in our previous study of Japanese men with prostate cancer, we found that they had a low prevalence of osteoporosis that was not increased by ADT.[7] These observations led us to hypothesize that Caucasian and Japanese men with prostate cancer may differ in terms of the influence of ADT on BMD due to racial and/or environmental differences. Because our previous study only examined a relatively small number of Japanese patients with prostate cancer, and the 58 ADT-treated patients had been treated for only a relatively short duration, in the current study we recruited larger numbers of Japanese patients with prostate cancer (n = 201) who had received ADT for a longer duration (average, 35.3 months). We then analyzed the effect of ADT on their BMD. In addition, to determine the influence of ADT on serum bone metabolic variables, we measured

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amino-terminal telopeptide (NTx) and carboxy-terminal telopeptide of type-I collagen (ICTP).

MATERIAL AND METHODS

Subjects

This cross-sectional study consisted of 201 native Japanese patients with prostate cancer. These patients comprised 113 ADT-treated and 88 hormone-naive patients, who were treated at the Akita University Medical Center from December 2006 through to March 2009. Of the 113 ADT-treated patients, 43 and 70 did and did not have bone metastasis, respectively. Patients with bone metastases in the lumbar spine or the hip joint were not included in this study as these were the regions we used to measure BMD. All prostate cancer patients were diagnosed according to histologic analysis of specimens obtained by transrectal needle biopsy or transurethral resection of the prostate performed to alleviate voiding symptoms. The ADT patients without bone metastasis were treated with combined androgen blockade (CAB) therapy using bicalutamide (80 mg/d) together with luteinizing hormone-releasing hormone (LH-RH) analog and/or surgical castration (n = 34), LH-RH analog monotherapy (n = 28), or bicalutamide monotherapy (n = 6). Among the patients, 2 were treated with CAB therapy using LH-RH analog and estramustine phosphate for a maximum of 3 months. In addition, 27 of the 43 ADT-treated patients with bone metastasis (62.8%) had also received estramustine phosphate during their treatment process. Among these ADT-treated patients, 5 patients (11.6%) with bone metastasis and 27 (38.6%) without metastasis underwent local radiation therapy in their earlier disease course. None of the hormone-naive patients underwent radiation therapy. The prostate cancers were pathologically graded according to Gleason's histologic grading and the Tumor-Node-Metastatic system.[8,9]

BMD Measurements

BMD was measured in our hospital in 2006-2009 by dual-energy x-ray absorptiometry using a Delphi QDR (Hologic, Bedford, MA), as previously described.[7] The area of BMD in grams per square centimeter was measured at the posteroanterior spine (L2-L4) and the nondominant hip (total hip and femoral neck). Peak BMD, age-specific BMD, peak standard deviation (SD), and age-specific SD for dual-energy x-ray absorptiometry values were derived from the Hologic database for East Asian ethnicity (version 2.0; Hologic, Bedford, MA). BMD was expressed in SD units relative to the BMDs of young adult men (*T*-score) and age-matched men (*Z*-score). According to World Health Organization criteria, a normal BMD is defined as a *T*-score greater than −1 SD, osteopenia as a *T*-score between −1 and −2.5 SD, and osteoporosis as a *T*-score of −2.5 SD or less.[10] In this study, we used the *T*-score of the worst site to classify the patient, as previously described.[7]

Measurement of Biochemical Values

The serum levels of NTx (normal range, 9.5-17.7 nmol/L), ICTP (normal range, 1.6-3.8 ng/mL), intact parathyroid hormone (normal range, 15-65 pg/mL), prostate-specific antigen (PSA; normal range, <4 ng/mL), and testosterone (normal range, 2.0-7.6 ng/mL), and common laboratory blood and serum data were measured before breakfast at the time BMD was measured, as described previously.[7]

Statistical Analysis

Differences in the clinical and serum variables of the hormone-naive patients, the ADT-treated patients without bone metastasis, and the ADT-treated patients with bone metastasis were evaluated using the Student *t* test. Alternatively, the Mann–Whitney *U* test was used if the group variances were unequal or the dependent variables were non-normally distributed and not transformable. The groups were also compared with regard to the prevalence of normal BMDs, osteopenia, osteoporosis and the respective treatment groups, and analyzed statistically by using the Kruskal–Wallis test. Nonparametric Spearman rank-order correlation coefficients were calculated to investigate the relationship between BMD, *T*-score, and *Z*-score, and treatment period. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 13.0; SPSS, Inc., Chicago, IL) and two-sided $P < .05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics

The 201 patients were divided into hormone-naive patients (n = 88), ADT-treated patients without bone metastasis (n = 70), and ADT-treated patients with bone metastasis (n = 43), and their characteristics, including their age, body mass index, biopsy Gleason score, and serum or blood levels of PSA, hemoglobin, albumin, lactate dehydrogenase, glucose, and testosterone, and the presence and duration of ADT, are summarized in Table 1. The ADT-treated patients were grouped into those who did and did not have bone metastasis because bone metastasis can artificially elevate BMD measurements, even in patients who do not seem to have bone metastases in the areas being measured. The ADT-treated patients without bone metastasis were significantly older than the other 2 groups ($P < .001$ and .038, respectively), while the ADT-treated patients with bone metastasis had higher serum PSA values and lower hemoglobin, albumin, and blood glucose levels than those without bone metastasis ($P = .014$, $< .001$, $< .001$, and .008, respectively). The hormone-naive patients had significantly higher body mass index and serum levels of testosterone than the ADT-treated patients without bone metastasis ($P = .034$ and $< .001$, respectively). However, all 3 groups were similar in biopsy Gleason scores (Table 1).

Comparison of the BMD, *T*-Scores, and *Z*-Scores of the Hormone-Naive and ADT-treated Patients With or Without Bone Metastasis

The ADT-treated patients without bone metastasis had significantly lower BMD values and *T*-scores at all 3 sites than the hormone-naive patients (Table 2). The ADT-treated patients without bone metastasis also had significantly lower *Z*-scores at the lumbar spine and total hip than the hormone-naive patients (Table 2). These results suggest ADT decreased BMD in these patients. In contrast, the ADT-treated patients with bone metastasis had significantly higher BMD values, *T*-scores, and *Z*-scores

Table 1. Comparison of the characteristics of the 3 groups of patients with prostate cancer

	Hormone-Naive Prostate Cancer Patients	ADT-treated Prostate Cancer Patients Without Bone Metastasis	ADT-treated Prostate Cancer Patients With Bone Metastasis	P*	P†
N	88	70	43		
Age (y)	65.1 ± 9.7	74.1 ± 6.2	71.1 ± 7.7	<.001	.038
BMI (kg/m^2)	24.2 ± 3.1	23.2 ± 3.0	23.9 ± 3.9	.034	.336
Biopsy Gleason score	7.4 ± 1.2	7.7 ± 1.4	8.0 ± 1.3	.244	.291
PSA (ng/mL) at diagnosis	12.6 ± 10.3	25.2 ± 28.5	851 ± 2124	.271	.014
Hemoglobin (g/dL)	12.8 ± 1.6	12.3 ± 1.6	10.8 ± 1.9	.111	<.001
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	3.7 ± 0.4	.334	<.001
LDH (IU/L)	174 ± 32	201 ± 62	444 ± 1101	<.001	.161
Blood sugar (g/dL)	117 ± 39	125 ± 35	106 ± 35	.148	.008
Testosterone (ng/mL)	4.1 ± 2.1	0.8 ± 0.8	0.8 ± 0.7	<.001	.46
Duration of ADT (mon)	—	30.7 ± 25.8	40.3 ± 19.4	—	.014

BMD = bone mineral density.
Values indicate means ± SD.
* Probability values of the differences between the hormone-naive patients and the ADT-treated patients without bone metastasis.
† Probability values of the differences between the ADT-treated patients with and without bone metastasis.

Table 2. Comparison of the BMDs, *T*-scores, and *Z*-scores of the 3 groups of patients with prostate cancer

	Hormone-Naive Prostate Cancer Patients	ADT-treated Prostate Cancer Patients Without Bone Metastasis	ADT-treated Prostate Cancer Patients With Bone Metastasis	P*	P†
N	88	70	43		
Age (y)	65.1 ± 9.7	74.1 ± 6.2	71.1 ± 7.7	<.001	.038
Lumbar spine					
BMD	1.060 ± 0.21	0.973 ± 0.212	0.973 ± 0.136	.008	.164
T-score	0.102 ± 1.502	−0529 ± 1.519	−0.585 ± 0.943	.006	.691
Z-score	0.663 ± 1.199	0.288 ± 1.101	0.156 ± 0.820	.034	.966
Femoral neck					
BMD	0.774 ± 0.133	0.716 ± 0.112	0.779 ± 0.109	.002	.002
T-score	−0.701 ± 1.049	−1.161 ± 0.833	−0.656 ± 0.855	.004	.003
Z-score	0.511 ± 1.090	0.280 ± 0.915	0.674 ± 0.967	.054	.034
Total hip					
BMD	0.916 ± 0.155	0.824 ± 0.130	0.911 ± 0.125	<.001	.001
T-score	−0.333 ± 1.163	−1.007 ± 0.977	−0.365 ± 0.934	<.001	<.001
Z-score	0.721 ± 1.110	0.332 ± 0.945	0.795 ± 0.983	<.001	.007

BMD = bone mineral density.
Values indicate means ± SD.
* Probability values of the differences between the hormone-naive patients and the ADT-treated patients without bone metastasis.
† Probability values of the differences between the ADT-treated patients with and without bone metastasis.

at the femoral neck and total hip than the ADT-treated patients without bone metastasis (Table 2). Notably, the average Z-scores of the ADT-treated patients (with or without bone metastasis) and the hormone-naive patients were positive in this study. We also observed this in our previous study.[7]

Prevalence of Osteoporosis and Osteopenia in the Hormone-Naive and ADT-treated Patients

We compared the prevalence of osteoporosis and osteopenia in the hormone-naive patients and the ADT-treated patients without bone metastasis (Fig. 1A). On the basis of the worst site showing a low *T*-score, the prevalence of osteoporosis and osteopenia for the hormone-naive prostate cancer patients (n = 88) were 4.5% (4 patients) and 31.8% (26 patients), respectively. In contrast, for the prostate cancer patients who had been treated with ADT for less than 2 years (n = 33), the respective prevalence were 12.1% (4 patients) and 48.4% (16 patients). For the prostate cancer patients who had been treated with ADT for more than 2 years (n = 37), the respective prevalence were 10.8% (4 patients) and 54.1% (20 patients). The prevalence did not differ significantly. Thus, although the ADT-treated patients without bone metastasis had significantly lower BMD values, *T*-scores, and even Z-scores than the hormone-naive patients, their ADT treatment (on average 30.7 months) did not elevate the prevalence of osteoporosis. The BMDs of the CAB- and LH-RH monotherapy–treated patients did not differ significantly.

Association Between Duration of ADT and BMDs, *T*-Scores, and *Z*-Scores of Patients With Nonmetastatic Prostate Cancer

We investigated the association between the duration of ADT and the BMDs, *T*-scores, and Z-scores of the ADT-treated patients with nonmetastatic prostate cancer (Fig. 1B). The duration of ADT did not correlate significantly

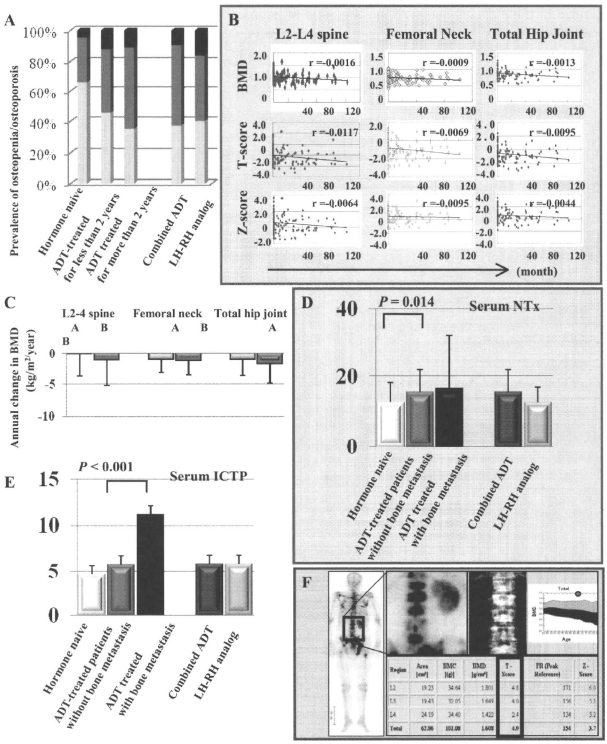

Figure 1. Relationship between androgen-deprivation (ADT) therapy and bone mineral density (BMD) of patients with prostate cancer. **(A)** The frequencies of osteoporosis (black bars), osteopenia (dark gray bars), and normal BMD (light gray bars) of the ADT-treated patients without bone metastasis and the hormone-naive patients. **(B)** Association between the duration of ADT of patients without bone metastasis and their BMDs **(B)**, *T*-scores (**T**), and *Z*-scores (**Z**) of the lumbar spine, femoral neck, and total hip joints. **(C)** Comparison of the annual BMD loss in the preceding year at the lumbar spine, femoral neck, and total hip joints of the hormone-naive patients (light gray bars) and the ADT-treated patients without bone metastasis (dark gray bars). Comparison of the serum levels of the bone resorption markers, NTx **(D)** and ICTP **(E)**, of the hormone-naive patients, the ADT-treated patients without metastasis, and the ADT-treated patients with bone metastasis. **(F)** Typical BMD measurement of the prostate cancer patient with bone metastasis.

with BMD for all 3 sites measured (L2-L4 spine, femoral neck, and total hip join; $r = -0.0016$, -0.0009, and -0.0013, respectively). We also analyzed the bone loss during 1 year in the ADT-treated patients (n = 25) and hormone-naive patients (n = 16) whose BMD had been measured twice with a 1-year interval in the preceding year. In both groups, their average BMDs had decreased over the year, but the 2 groups did not change significantly with regard to annual change in BMD (Fig. 1C).

Influence of ADT on Serum Variables and Bone Metabolism

Next, to determine the effect of ADT on serum variables associated with bone metabolism, we compared the hormone-naive patients, the ADT-treated patients without metastasis, and the ADT-treated patients with metastasis with regard to these variables. As shown in Fig. 1D, the ADT-treated patients without metastasis had significantly higher serum levels of NTx, which reflects bone resorption, than the hormone-naive patients ($P = .014$).

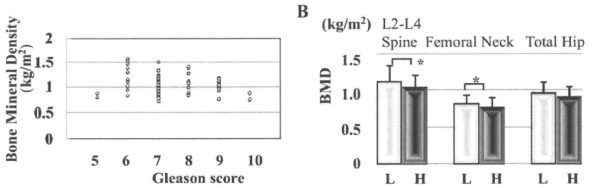

Figure 2. Relationship between the bone mineral densities and Gleason scores of the hormone-naive patients with prostate cancer. **(A)** Relationship between the bone mineral densities and Gleason scores. **(B)** Comparison of the bone mineral densities of patients with low (**L**) and high (**H**) Gleason scores. Gleason scores ≤7 (low, n = 49) vs >7 (high, n = 31). * $P < .05$.

However, these 2 groups did not differ significantly in any of the other serum variables. In addition, the ADT-treated patients with bone metastasis had significantly higher serum levels of ICTP, which also reflects bone resorption, than the ADT-treated patients without bone metastasis (Fig. 1E, $P < .001$). The CAB-treated patients and the patients treated with LH-RH analog alone did not differ in either NTx or ICTP levels.

Relationship Between Serum Testosterone Levels, BMDs, and Biopsy Gleason Scores

That all groups exhibited average Z-scores in this study suggested that these prostate cancer patients had higher BMDs than age-matched East Asian men. Therefore, we investigated the BMDs and other characteristics of these patients further. Of the 88 hormone-naive patients, the serum testosterone levels, BMDs, and biopsy Gleason scores were available for 80 patients. We first examined the relationship between the serum testosterone level and biopsy Gleason score but did not find a significant association (data not shown). However, patients with high Gleason scores tended to have lower BMDs than those with low Gleason scores (Fig. 2A). Patients with high-risk locally advanced prostate cancer are defined by PSA >20 ng/mL, Gleason score >7, and clinical stage T3/T4. In this group of patients, reported rates of disease-free survival after local therapy range from 30% to 50%.[11,12] Therefore, we compared the BMDs of the patients who had Gleason scores of ≤7 with those whose Gleason scores exceeded 7. The patients who had high Gleason scores had significantly lower BMDs than those with lower Gleason scores (Fig. 2B).

COMMENT

Our previous study showed that both ADT-treated and hormone-naive Japanese patients with prostate cancer have low rates of osteoporosis.[7] Here, we found that, although the ADT-treated patients did have significantly lower BMD values, T-scores, and Z-scores than the hormone-naive patients (Table 2), there was no concomitant significant increase in the prevalence of osteoporosis in the ADT-treated patients (Fig. 1A) who had been treated with ADT for an average of 30.7 months. On the contrary, other studies of ADT-treated patients with prostate cancer in western countries found they had a high incidence of osteoporosis,[13-15] For example, Morote et al[14] reported that 35.4% and 45.2% of hormone-naive patients had osteoporosis and osteopenia, respectively, while 42.9% and 39.3% of patients who had been treated with ADT for 2 years suffered from osteoporosis and osteopenia, respectively. In this study, we again found that this was not true for Japanese patients with prostate cancer.

Osteoblastic metastatic lesions, which frequently occur in patients with bone metastasis and prostate cancer, may artificially increase the BMD score (Fig. 1F). This observation led us to exclude several typical cases with bone metastasis from the current and previous studies.[7] However, although we did not detect any significant differences between ADT-treated prostate cancer patients with and without bone metastasis with regard to BMD or serum levels of bone metabolic markers in our previous study,[7] in the present study, we found that the ADT-treated patients with bone metastasis had significantly higher BMD values than the ADT-treated patients without bone metastasis (Table 2). These results suggest that bone scans may fail to detect small metastatic bone lesions in the measured sites that can artificially elevate the BMD measurements. Alternatively, because 62.8% of the patients with bone metastasis were given estramustine phosphate during their treatment process, it is possible that this nitrogen mustard-conjugated estrogen may have helped to prevent ADT-induced bone loss in these patients.

The fact that the hormone-naive and ADT-treated patients with and without bone metastasis had positive average Z-scores indicates that the average BMDs of the patients in this study were higher than those of age-matched East Asian controls. Because the total hormonal environment during life affects BMD, this observation suggests that Japanese patients with prostate cancer may have had increased testosterone levels that led to higher than normal BMDs. These abnormal hormonal levels