IL-2は北米では高用量投与で特に5%前後に長期CRを得られるため，標準治療の1つとなっている．しかしながら高用量と低用量の比較試験で，低用量にすると奏効率は低下するが生存期間は差がなく，高用量投与のエビデンスは十分とはいえない．

b. 悪性黒色腫

IFN-αは転移性黒色腫においては奏効率10%台で，薬物療法にIFN（± IL-2）を加えると奏効率は改善するが，生存期間は改善しなかった．一方，術後補助療法のメタアナリシスにおいて，高リスクの患者への高用量投与により，有意な再発率の低下（HR 0.82），死亡率の低下傾向（HR 0.89）が認められている．なお，これらの試験の多くはわが国で承認されていない高用量（1,000万～2,000万）静注を用いており，またわが国で悪性黒色腫に対して適応が承認されているのはIFN-βだけである．

IL-2は高用量投与により奏効率16%，CR 6%，またCR例の59%は7年間無増悪であり完治の可能性があると報告されている．低用量については高用量に比較して効果は低いようである．

c. 血液疾患

1）ヘアリー細胞白血病（hairy cell leukemia）

IFN-αにより奏効率50～90%，CR 4～30%，PR 43～86%，6年生存率は85%と報告されている．しかしpurine analogueにより70%以上のCR率が得られることから使われなくなった．

2）皮膚T細胞リンパ腫

IFN-αは最も有効な薬剤の1つであり，奏効率は45～55%，CR 10～27%でIFN-β，γもほぼ同様の効果をもつ．特にPUVAと併用するとstage IB～IIAでは奏効率80%以上とされる．

3）慢性骨髄性白血病（CML）

IFN-αはCML（chronic myelogenous leukemia）慢性期において60～80%に血液学的寛解，一部に細胞遺伝学的寛解（BCR/ABLの消失）が得られる．しかしimatinibが高率に細胞遺伝学的寛解をもたらし，生存期間もIFNより改善することが報告され，用いられなくなった．

4）多発性骨髄腫

IFN-αの有効性はメタアナリシスにおいてもIFN投与により奏効率，生存期間が改善されるがその差は約4ヵ月で，副作用を考えるとメリットがあるかどうかの判断はむずかしい．最近bortezomib，thalidomide，lenalidomideなどの新たな薬剤が導入され，用いられなくなっている．

d. その他のがん腫

1）悪性脳腫瘍

星状細胞腫（astrocytoma），神経膠腫（glioma）に対してIFN-α，βが試みられているが，明らかな有効性のエビデンスはない．

2）血管肉腫

わが国で承認されているがほとんど放射線照射または薬物療法との併用で，多数例における単独療法のデータはない．

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ORIGINAL ARTICLE

Prospective evaluation of incidence and severity of oral mucositis induced by conventional chemotherapy in solid tumors and malignant lymphomas

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Abstract
Purpose Oral mucositis (OM), a complication frequently associated with cancer chemotherapy, may decrease treatment efficacy due to dose reduction or impair the patient's quality of life. The purpose was to determine the incidence and severity of OM and its sequelae in patients receiving conventional chemotherapy for various malignancies.
Methods Two hundred twenty-seven patients (male, 33%; female, 66%) who received chemotherapy for head and neck cancer, esophageal cancer, colorectal cancer, breast cancer, and malignant lymphomas at the Cancer Institute Hospital between January 2007 and December 2008 were examined with questionnaires, prospectively.
Results The incidence of OM was highest in patients with breast cancer (76.5%), then head and neck cancer (67.7%), colorectal cancer (63%), esophageal cancer (57.8%), and malignant lymphoma (42.9%). However, patients who experienced severe OM (≥grade 3) were rare: at most 4.8%. The high-risk regimens for OM were TPF (85.7%), FOLFIRI (80%), CAF (78.8%), AC (70.6%), and FOLFOX (60%). OM was associated with gastrointestinal adverse events, anorexia, diarrhea, and dysphagia, which aggravated quality of life. There was no correlation between incidence of OM and prior therapy, PS, oral care, or laboratory data. There was no statistically significant correlation between OM and overall survival. The predictive factor was history of OM in previous chemotherapy.
Conclusion OM frequently occurs in patients with various tumors receiving conventional chemotherapy. Despite low-grade OM, they might cause gastrointestinal adverse events. Adequate preventive treatment for OM is required depending on each chemotherapy regimen and each patient's OM history.

Keywords Oral mucositis · Incidence · Severity · Chemotherapy

Introduction

Aggressive combined modality therapies are used in patients with various malignancies and can help them achieve longer survival but may be accompanied by increasing frequency of adverse events. Of these, oral mucositis (OM) is one of the most frequent complications induced by chemotherapy, with or without radiotherapy [3]. Serious OM can cause considerable pain requiring opioid analgesia, sepsis in neutropenic patients [8], and dysphagia requiring placement of feeding tubes. Thus OM can limit the tolerated dose of chemotherapy with or without radiotherapy, which can in turn affect both progression-free survival and overall survival [7]. In 2004, the first evidence-based clinical guidelines for OM prevention and treatment were published by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology [10]. Until then, OM had been underestimated. Therefore, major progress in recognizing OM as one of the important adverse events

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of chemotherapy and elucidating epidemiology, pathology, and clinical outcomes of OM has occurred recently. To prevent OM, the use of palifermin, keratinocyte growth factor-1, is recommended as level I evidence/grade A in patients with hematological malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation. Other agents, such as Saforis (L-glutamine in a proprietary oral drug delivery system) [4] and RK-0202 (*N*-acetylcysteine in a proprietary mouth rinse formulation) are being developed [2]. These agents are expensive and may themselves cause adverse events including rash, pruritus, erythema, mouth and tongue disorders, as well as taste alteration. Therefore, we need to be careful in choosing these medications [11]. OM may occur in 70% to 100% of patients who have undergone high-dose chemotherapy plus total body irradiation followed by hematopoietic stem cell transplantation [9, 11] and in up to 100% of patients with head and neck cancer receiving chemoradiotherapy [6, 12]. However, there is no prospective study of the incidence of OM induced by standard chemotherapy for common solid tumors and malignant lymphomas. The aim of this study was to clarify the OM incidence and severity in patients with common solid tumors and malignant lymphomas and predict which patients would be indicated for emerging preventing medicines of OM.

Patients and methods

Patients

This study enrolled patients who were at least 20 years of age and had head and neck squamous cell cancer (HNSCC), esophageal cancer, breast cancer, colorectal cancer, gastric cancer, malignant lymphoma, or cancer of unknown primary site. They were all scheduled to undergo conventional chemotherapy for each cancer with or without radiotherapy from January 2007 to December 2008. Patients included were examined by self-report questionnaires about oral care, onset of OM, and gastrointestinal complications of anorexia, diarrhea, or dysphagia. OM was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) by clinical physicians. Patients were surveyed for detailed medical history, complete physical examination, blood counts, and chemistry profiles. The institutional review board at Cancer Institute Hospital approved the study protocol; all patients gave written informed consent before all study-related procedures. We excluded patients who gave inadequate consent or withdrew consent, died before chemotherapy, or were lost for follow-up.

Treatment regimens and OM prophylaxis

Patients were treated by conventional chemotherapy for each pathologically confirmed primary malignancy. TPF regimen (docetaxel at a dose of 75 mg/m^2 i.v. on day 1, cisplatin at a dose of 75 mg/m^2 i.v. on day 1, and fluorouracil (5-FU) at a dose of 750 mg/m^2/day i.v. as a continuous infusion on days 1 to 5 were administered every 3 weeks) was used for patients with head and neck cancer. FOLFIRI regimen (irinotecan at a dose of 150 mg/m^2 i.v. on day 1, leucovorin at a dose of 200 mg/m^2 i.v. on day 1 followed by bolus 5-FU 400 mg/m^2, and a 46-h infusion of 5-FU at a dose of 2400 mg/m^2 on days 1 to 2 were administered every 2 weeks) or FOLFOX 4 regimen (oxiliplatin at a dose of 85 mg/m^2 i.v. on day 1, leucovorin at a dose of 100 mg/m^2 i.v. on days 1 to 2, followed by bolus 5-FU 400mg/m^2, and a 46-h infusion of 5-FU at a dose of 1200 mg/m^2/day as a continuous infusion on days 1 to 2 were administered every 2 weeks) were used for patients with metastatic colorectal cancer. CAF regimen (cyclophosphamide at a dose of 500 mg/m^2 i.v. on day 1, doxorubicin hydrochloride at a dose of 50 mg/m^2 i.v. on day 1, and 5-FU at a dose of 500 mg/m^2 intravenously on days 1 and 8 were administered every 3 weeks) and AC (doxorubicin hydrochloride at a dose of 60 mg/m^2 i.v on day 1 and cyclophosphamide at a dose of 600 mg/m^2, i.v. on day 1 were administered every 3 weeks) were used for patients with breast cancer. R-CHOP regimen (rituximab at a dose of 375 mg/m^2 i.v. on days 1, 8, and 15, cyclophosphamide at a dose of 750 mg/m^2 i.v. on day 1, doxorubicin hydrochloride at a dose of 50 mg/m^2 i.v. on day 1, vincristine sulfate at a dose of 1.4 mg/m^2 i.v., up to a maximal dose of 2 mg on day 1, and prednisone at a dose of 50 mg/m^2 i.v on day 1 followed by oral intake on days 2 to 5 every 3 weeks) was administered to patients with diffuse large B cell lymphoma; weekly rituximab administration was a clinical trial setting. TC regimen (carboplatin at an area under the curve dose of 6 mg/ml per minute and paclitaxel 200 mg/m^2 i.v. on day 1 every 3 weeks) was used for cancer of unknown primary site. Other regimens used for a few patients (at most three) were excluded from the summary table showing the OM incidence rate. Patients received some OM prophylaxis, including mouthwashes, gargling with sodium azulene sulfonate.

Endpoints

Primary endpoints were the incidence of OM of CTCAE at any grades and severity among each cancer patients. Secondary endpoints included the 2-year overall survival.

Statistical analysis

A chi square test for contingency tables was used to compare OM incidence in Table 2. Kruskal–Wallis test was

Table 1 Baseline patient characteristics

Total number of patients	227
Sex, no. (%)	
Male	76 (33%)
Female	151 (67%)
Age, years	
Median	57
Range	23–86
Diagnosis, no. (%)	
Head and neck squamous cell cancer	31 (14%)
Esophageal cancer	13 (6%)
Breast cancer	102 (50%)
Colorectal cancer	27 (12%)
Malignant lymphoma	49 (22%)
Cancer of unknown primary site (CUP)	5 (2%)

used to compare the incidence rate by primary focus of cancer and regimens. The mean data of C-reactive protein (CRP), white blood cell counts, and albumin concentration were calculated and compared between patients with and without OM using unpaired Student's t test. Differences were assessed with two-sided tests, with an alpha level of 0.05. The survival of patients with and without OM was estimated by Kaplan–Meier curves and was compared using the logrank test.

Results

Patients

A total of 237 cancer patients who were scheduled to receive chemotherapy or chemoradiotherapy were recruited into the study between January 2007 and December 2008. Of these, ten (4%) were ineligible (inadequate enrollment, $n=3$; lost for follow-up, $n=2$; withdrawal of consent, $n=1$; inadequate consent, $n=1$; discontinued treatment, $n=1$; death before treatment, $n=1$; unknown, $n=1$) Baseline patient characteristics at enrollment are listed in Table 1.

OM incidence and patient background

First we investigated which patient's background or OM prophylaxis affected the incidence rate of OM (Table 2). There was no significant difference in OM incidence rate between primary and recurrent cases, the presence or absence of past history of cancer, RT, chemotherapy, surgery, or oral cavity. Neither did oral disease, self-oral care, dentures, untreated teeth, nor age affects outcomes.

OM incidence rate and severity by primary focus of cancer

Next we compared OM incidence rate with primary focus of cancer (Fig. 1). Among the total study population, 82 (36%) of the 227 patients did not experience any OM during the courses of the protocol treatment. Seventy-eight (76.5%) of 102 breast cancer patients had grades 1 to 3 OM during four courses of treatment, which was the highest OM incidence rate. Furthermore, 21 (67.7%) of 31 HNSCC patients, 17 (63%) of 27 colorectal cancer patients, 7 (57.8%) of 13 esophageal cancer patients, 21 (42.9%) of 49 malignant lymphoma patients, and 1 (20%) of 5 cancer of unknown primary patients developed OM, respectively. The grades 2 and 3 OM incidence rates were higher in patients with HNSCC and breast cancer at 26% (11 of 42) and 23% (40 of 142), respectively. However, overall, only three patients (two with HNSCC and one with breast cancer) developed severe OM (≥grade 3), which showed that the severity of OM induced by conventional chemotherapy is not serious.

OM incidence rate by regimens

Then we evaluated OM incidence rate by regimens and individual anticancer agents. The high-risk regimens for OM were TPF (85.7%), FOLFIRI (80%), CAF (78.8%),

Table 2 Correlation between OM incidence and prior therapy or oral condition

	OM Incidence (%) Yes/No	p value
Newly diagnosed cancer/recurrence	63.4/64.5	1.00
Prior history of cancer	64.1/57.9	0.62
Prior history of radiation	63.6/63.0	1.00
Prior history of chemotherapy	63.9/65.6	1.00
Prior history of surgery	58.6/70.7	0.07
Prior history of oral cavity surgery	63.3/75	0.54
Denture (full/partial/no)	100/52.9/65.1	0.34
Untreated teeth	63.9/66.7	1.0
Self oral care/by nurse	64.0/50.0	1.0
Oral wound before chemotherapy	64.0/62.05	1.0

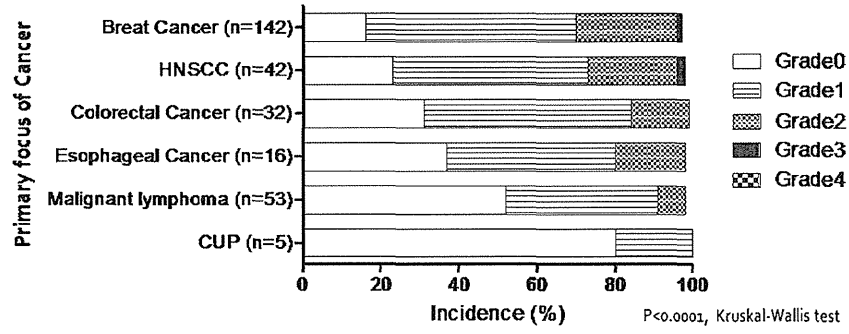

Fig. 1 OM incidence rate according to primary focus of cancer. OM was graded according to NCI CTCAE ver 3.0. *HNSCC* head and neck squamous cancer, *CUP* cancer of unknown primary

AC (70.6%), and FOLFOX (60%) in order (Fig. 2). Interestingly, AC regimen (doxorubicin hydrochloride and cyclophosphamide) for breast cancer showed the higher rate of OM, while CHOP regimen (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) for malignant lymphoma showed a much lower OM frequency (40.9%). These data indicated that 5-FU containing regimens and adriamycin–cyclophosphamide for breast cancer were high-risk regimens for OM onset.

OM incidence was related to the previous occurrence of OM

Next, the difference of OM incidence in patients with or without OM in previous chemotherapy through four cycles was investigated (Fig. 3). Patients who experienced OM in a previous cycle tended to develop OM again compared with patients without previous OM. These results imply that the increased incidence is not only related to drugs used in chemotherapy regimens but also to host factors.

OM was associated with gastrointestinal adverse events

We evaluated the correlation between gastrointestinal adverse events and OM incidence rate, to clarify whether OM influences a patient's quality of life. The patients with OM had higher incidence rate of gastrointestinal adverse events including anorexia (70.2% vs. 40.1%, $p<0.001$), diarrhea (32.5% vs. 16.3%, $p<0.001$), and dysphagia (29.1% vs. 9.9%, $p<0.001$) significantly than patients without OM. Patients who had gastrointestinal events were impaired in nutrition and performance status, which may worsen their quality of life.

Laboratory assessments

Laboratory data regarding neutrophil count, serum albumin level, and serum C-reactive protein (CRP) before treatment were assessed to have prognostic power on the onset of OM or not. All of them were found to be similar at day 1 of chemotherapy in patients with or without OM. Unexpectedly, serum CRP level under the lower limit of normal was the only factor found to be correlated with OM ($p=0.01$). However, the multivariate analysis showed no significant difference of CRP level in these two groups.

Overall survival at 2 years had no significant difference

Finally, the long-term follow-up data for disease outcomes were available for 257 patients. The median follow-up duration was 24 months. The 2-year overall survival rate was 74% in patients with OM, 84% in patients without OM

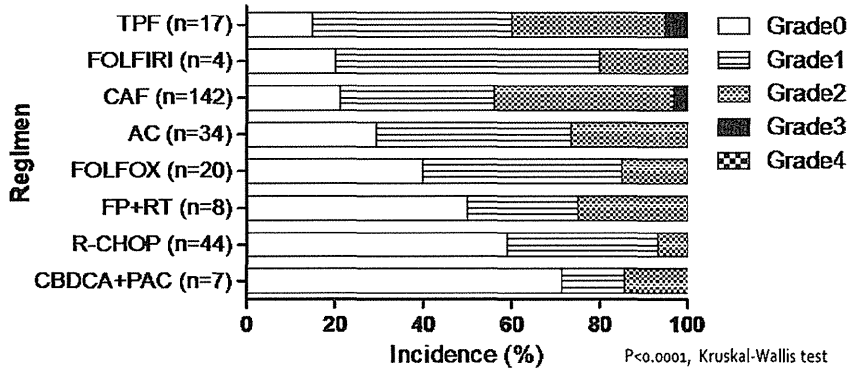

Fig. 2 OM incidence rate according to regimen. OM was graded according to NCI CTCAE ver 3.0. *TPF* docetaxel, cisplatin, 5-FU; *FOLFIRI* 5-FU, leucovorin, irinotecan (CPT11); *CAF* 5-FU, doxorubicin and cyclophosphamide; *AC* doxorubicin, cyclophosphamide; *FOLFOX* 5-FU, leucovorin, oxaliplatin, *FP+RT* 5-FU, cisplatin, radiation; *R-CHOP* rituximab, doxorubicin, vincistine, cyclophosphamide, prednisone; *CBDCA+PAC* carboplatin, paclitaxel

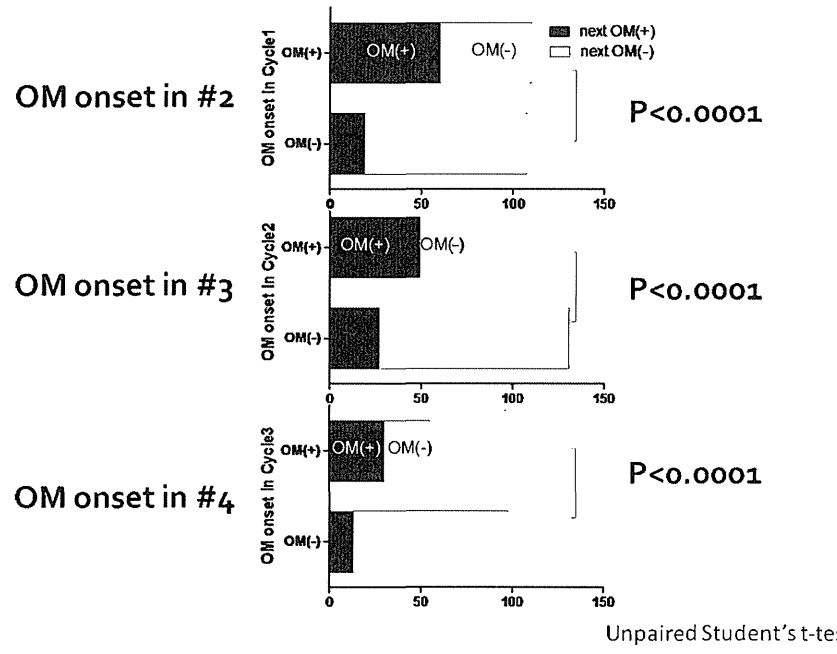

Fig. 3 OM incidence rate stratified by cycle number. *Black or white bar* shows the number of patients with OM or without OM, respectively

(Fig. 4). The Kaplan–Meier estimate curves for overall survival time showed no significant difference between the patients with OM and those without OM (p=0.651), with no median for the study reached.

Discussion

The effects of chemotherapy-induced OM had been underestimated until the first guidelines were published by Sonis et al. in 2004[10], updated by Peterson in 2008 [6]. However, a retrospective study of 599 patients who developed myelosuppression with chemotherapy showed that severe OM is associated with an increased risk of malnutrition or systemic infections, which can decrease the dose intensity of chemotherapy and may be life threatening [1].

In the present study, firstly we have shown that OM occurs more frequently than we expected in patients receiving conventional chemotherapy; 64% of the patients experienced OM. However, severe OM (grade 3 or more by CTCAE v.3.0) was rare. In previous retrospective studies, the frequency of severe OM of grade 3 or more was reported in the range from 1% to 13% in patients with non-Hodgkin lymphoma and breast, lung, or colorectal cancers who were treated with standard chemotherapy [4]. The previous data are consis-

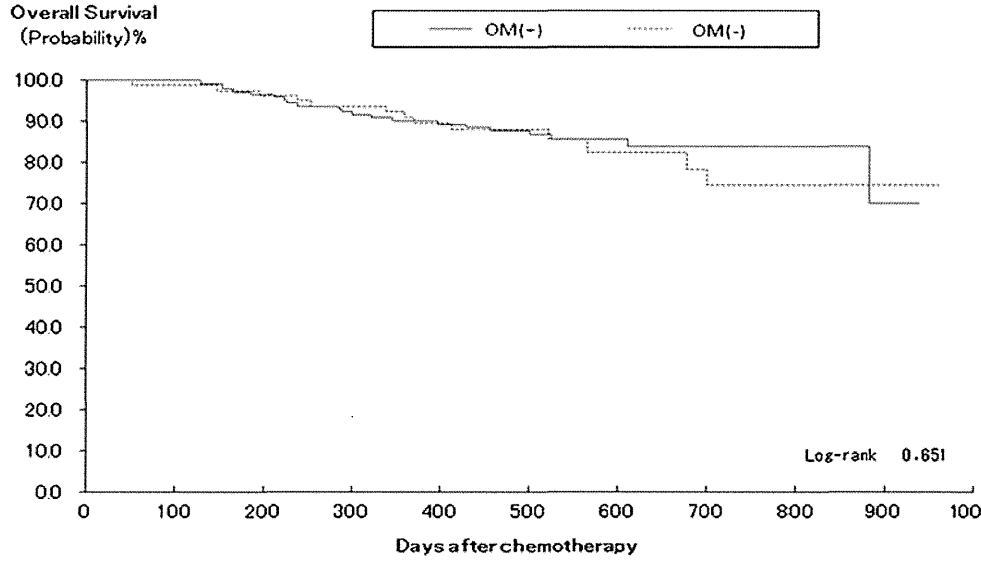

Fig. 4 Kaplan–Meier estimates of overall survival according to occurrence of OM

tent with our study; patients who developed severe OM in this study were from 0% to 4.8%.

However, low-grade OM occurred in at least 40% of patients with non-Hodgkin lymphoma and breast, head and neck, esophageal, colorectal cancers, or cancer of unknown primary site. Even patients who developed low-grade OM suffered from gastrointestinal adverse events including anorexia, diarrhea, and dysphagia. These adverse events impaired their quality of life and motivation for chemotherapy. This was among the first studies to show that low-grade OM can be accompanied with gastrointestinal adverse events.

Among the various chemotherapy regimens, those with higher risk for OM were 5-FU-containing regimens such as TPF, CAF, or FOLFIRI. 5FU has been reported to cause grade 3–4 OM with incidence of more than 15% [10]. The percentage of severe OM in this study was lower than the previous data. It might be due to careful oral care including dentists' check-up. However, 5-FU is of particular importance as the cause of chemotherapy-induced OM.

Another interesting point was the difference of OM incidence between R-CHOP regimen for non-Hodgkin lymphoma and AC regimen for breast cancer: 40.9% vs. 70.6%. It may be due to different patient backgrounds such as age and sex. In addition, the difference of supportive care should be considered as a cause of this difference. Sixteen milligrams of dexamethasone on day 1 and 8 mg on days 2–3 was used as an antiemetic agent with the AC regimen, while prednisolone 60 mg/m^2 on days 1–5 were used in R-CHOP regimen. This may imply that sufficient dose of prednisolone is more effective as an anti-mucositis agent than dexamethasone; however, in previous study, 40 mg/day prednisone had no difference in the degree of maximum mucositis expression and median duration of mucositis as compared with placebo group despite favoring shorter treatment interruptions in prednisone arm in prospective study [5]. Although we are in doubt regarding anti-OM effect by prednisolone, this is something we need to look at more closely in a next study.

Then we tried to find biomarkers for OM onset to choose patients for emerging preventing medicine, but we were unable to find one. Nevertheless, patients who experienced OM in previous cycle of chemotherapy showed a strong tendency for next OM onset. This is also the first evidence to show strong association of this tendency. To date, there is no significant predictive factor, so we have to wait to see OM onset after the administration of the first cycle of chemotherapy.

Finally, overall survival at 2 years showed no significant difference between patients with or without OM (Fig. 4). Relative dose intensity in patients with or without OM did not differ significantly because the grade of OM was mostly low. That was the reason why OM in this study did not affect survival.

This is a small and short-period study by a single institute, and the numbers of patients in different malignancies were variable. However, this is the first prospective and comprehensive study about OM induced by chemotherapy.

In conclusion, we conducted a prospective study to investigate OM incidence and severity with conventional chemotherapy. OM incidence was from 26% to 86%, varying according to regimens, but severe (grade 3 or more) OM was rare. Management of OM is important throughout chemotherapy not only for patients' quality of life but also on effective chemotherapy, because even low grade OM is associated with gastrointestinal AE. We suggest that preventive medicine should be used for high-risk patients of low-grade OM. Further study is warranted to investigate whether emerging agents for prevention of OM, such as palifermin, will be effective for high-risk patients: (1) patients with previous OM onset and (2) patients scheduled to undergo 5-FU-containing regimens and AC regimen for breast cancer.

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CLINICAL TRIAL

Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month results

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Abstract Aromatase inhibitor-associated bone loss has not been proved in the Japanese or Asian women. The aim of this study was to evaluate an upfront or delayed strategy of bone protection therapy with zoledronic acid administered at 4 mg every 6 months in postmenopausal Japanese women with early breast cancer to compare with results of the Z-FAST and ZO-FAST studies in western countries. Postmenopausal women with hormone receptor positive early breast cancer receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (L_2–L_4) bone mineral density (BMD) decreased to less than young adult mean −2.0SD or when a nontraumatic fracture occurred. The primary endpoint of this study was to compare the percent change in L_1–L_4 BMD at 12 months between the groups. Secondary endpoints included percent changes in L_2–L_4 and total hip (TH) BMD. The upfront and delayed groups included 94 and 95 patients, respectively. At 12 months, L_1–L_4, L_2–L_4, and TH BMD significantly decreased by 2.0, 2.4, and 2.4%, respectively, in the delayed group. L_1–L_4 BMD was 4.9% higher in the upfront group than in the delayed group (95% CI 3.9–5.8%; $p < 0.001$). L_2–L_4 BMD was 5.6% higher (95% CI 4.5–6.6%; $p < 0.001$), and TH BMD was 4.4% higher (95% CI 3.3–5.4%; $p < 0.001$). At 12 months, upfront zoledronic acid therapy prevented bone loss in postmenopausal Japanese women who were receiving adjuvant letrozole, confirming the Z-/ZO-FAST study results in western populations.

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Introduction

Third-generation aromatase inhibitors such as letrozole, anastrozole, and exemestane have shown to improve disease-free survival of postmenopausal endocrine-sensitive breast cancer patients compared with tamoxifen in several large clinical studies such as ATAC [1], BIG1-98 [2], or IES [3].

Adjuvant endocrine therapy with aromatase inhibitors causes complete depletion of estrogen, and increases bone metabolism suddenly and continuously, so may cause bone loss. In the large clinical studies, patients treated with aromatase inhibitors showed higher bone fracture rates than those treated with tamoxifen [4, 5, 6], and marked bone loss with aromatase inhibitor treatment has been shown in bone sub-studies of those large studies [7].

Oral bisphosphonates such as alendronate [8], ibandronate [9], or risedronate [10] have shown to prevent or improve postmenopausal osteoporosis. Some studies have also shown that those oral bisphosphonates prevent aromatase inhibitor-associated bone loss [11, 12]. However, oral bisphosphonates have some weak points such as low bioavailability due to low absorption, gastrointestinal adverse events (AEs), and low compliance [13].

In a clinical study for postmenopausal osteoporosis patients, once a year intravenous infusion of zoledronic acid 4 mg significantly increased bone mineral density (BMD) of lumbar spine (LS) and femoral bone [14]. Then a large clinical study comparing once a year intravenous infusion of zoledronic acid 5 mg versus placebo in postmenopausal osteoporosis patients showed that zoledronic acid significantly decreased spinal and femoral fracture rates for 3 years [15].

Clinical studies were performed to show whether zoledronic acid could inhibit bone loss with adjuvant aromatase inhibitor for early breast cancer patients in Northern America and Europe (Z-FAST and ZO-FAST) [16, 17]. Those studies compared BMD between upfront group who are treated with zoledronic acid every 6 months from the start of letrozole, and delayed group who are treated with zoledronic acid when BMD decreases to less than −2.0SD or fragility fracture occurs, in letrozole-treated breast cancer patients. Both the studies showed that upfront treatment with zoledronic acid significantly improved BMD of LS and femoral bone, and suppressed letrozole treatment-associated bone loss.

But in the Japanese or Asian women, aromatase inhibitor-associated bone loss has not been proved in the prospective study. In retrospective studies, Yoneda et al [18] reported no significant bone loss with 1-year treatment with anastrozole in Japanese women, and they speculated that Japanese women are less fat, and effects of aromatase inhibitors on bone mass might be less in lean women. In the Japanese subgroup study of TEAM (tamoxifen vs. exemestane), BMD of patients with tamoxifen and exemestane were not significantly different [19]. Furthermore, phase III study comparing tamoxifen versus switch from tamoxifen to anastrozole in Japanese postmenopausal breast cancer patients (N-SAS BC03) showed that fracture rate was not significantly different between two groups [20].

This study is designed to compare BMD of LS and femoral bone in upfront group who are treated with zoledronic acid every 6 months and delayed group who are treated with zoledronic acid after decrease of LS (L_2–L_4) BMD to less than −2.0SD of young adult mean (YAM) or occurrence of nontraumatic clinical fracture in hormone receptor-positive, clinical grade I–IIIA, postoperative postmenopausal breast cancer patients, who are planned to be treated with letrozole 2.5 mg per day as adjuvant endocrine therapy. This study will investigate whether letrozole decrease the BMD in Japanese women as the same level as the western women, and whether zoledronic acid can improve BMD and prognosis of letrozole-treated early breast cancer patients.

Patients and methods

Study patients

Inclusion criteria were as follows; (1) adequately diagnosed and treated invasive breast cancer defined as: 1. clinical stage I, II, or IIIA, 2. primary tumor was removed by an appropriate surgical procedure such as mastectomy or breast conserving surgery; (2) estrogen receptor (ER) and/or progesterone receptor (PgR) positive defined with immuno-histochemical staining; (3) postmenopausal status defined by one of the followings: 1. women >54 years with cessation of menses, 2. spontaneous cessation of menses within the past 1 year, and are amenorrheic in women <55 years, and according to the definition of "postmenopausal range" for FSH and estradiol level, 3. bilateral oophorectomy; (4) patients with a baseline LS: L_2–L_4 BMD of YAM −2.0SD or more; (5) patients who have no LS or total hip (TH) fracture; (6) ECOG performance status of ≤2; (7) adequate organ function; (8) the date of randomization must be within 12 weeks from completion of surgery or from completion of adjuvant chemotherapy (completion of chemotherapy is defined as completion of the last full course including recovery time); (9) patients

who have discontinued the following drugs known as affecting the skeleton more than 4 weeks: oral bisphosphonates, estrogen, raloxifene, calcitonin, vitamin K, activated vitamin D, ipriflavone, (10) a written informed consent is obtained.

Exclusion criteria were as follows: (1) patients with any clinical or radiological evidence of distant spread of their disease at any point before randomization, (2) patients with invasive bilateral breast cancer, (3) patients who have started adjuvant endocrine therapy, (4) patients who have received any endocrine therapy within the past 12 months, (5) patients who have received prior treatment with intravenous bisphosphonates within the past 12 months, (6) patients with the following diseases which may interfere with dual-energy X-ray absorptiometry (DXA) scan: severe scoliosis, hyperostosis, or sclerotic changes at the LS, other vertebral diseases, and calcification of abdominal aorta, (7) patients with previous or concomitant malignancy (not breast cancer) within the past 5 years, (8) current active dental problems including infection of the teeth or jaw, and recent (within 6 weeks) or planned dental or jaw surgery (e.g., extraction, implants), (9) other conditions judged as inappropriate for the study by the investigator.

Study design (Fig. 1)

In this open-label, multicenter, randomized study, all patients received letrozole 2.5 mg orally daily for 5 years or until relapse. Patients were randomly assigned to upfront or delayed zoledronic acid 4 mg or an adjusted dose based on renal function intravenous injection over 15 min every 6 months for 5 years. The upfront group received zoledronic acid after random assignment, whereas the delayed group received zoledronic acid when either post baseline LS (L_2–L_4) BMD decreases to YAM −2.0SD or less, or a nontraumatic clinical fracture occurred.

Patients were stratified according to adjuvant chemotherapy (yes or no) and baseline LS (L_2–L_4) BMD (normal: less than YAM −1.0SD or mild to moderate osteopenia: BMD between YAM −1.0SD, and YAM −2.0SD).

Primary endpoint of this study was the percent change in LS BMD (L_1–L_4) at 12 months in patients receiving upfront compared with delayed-start zoledronic acid. The secondary endpoints were the percent change in LS BMD (L_2–L_4), TH BMD and changes in serum N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) concentrations at 12 months. Additional secondary endpoints, including percent change in LS and TH BMD at 2, 3, 4, and 5 years; incidence of any clinical fracture at 3 years; time to disease progression, will be reported as these results become available.

BMDs of the LS and TH were evaluated at baseline and at 6, 12, 24, 36, and 48 months and at the final visit using either Hologic or Lunar DXA devices. All DXA devices were standardized and cross-calibrated using 4 Bio-Imaging Bona Fide Phamtoms.

Serum NTx and BSAP concentrations were evaluated at baseline and every 6 months during years 1–2, once at 36 and 48 months, and at the final visit.

AEs and disease progression were evaluated every 6 months. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The institutional review board or the ethics committee of the participating institutions approved the study. Informed consent was obtained from each patient before enrollment.

Statistical analysis

The study design used a 2-sample Student's t test, with power 80% and a significance level of $P = .05$ to detect a 4% difference in percent change in LS (L_1–L_4) BMD from baseline to 12 months between the groups. A sample size of 74 patients per treatment arm was required. To allow 20% dropout rate, at least 90 patients in each treatment are required.

The primary efficacy analysis was performed after all patients had passed the 12-month visit. An analysis of covariance model was used to compare differences

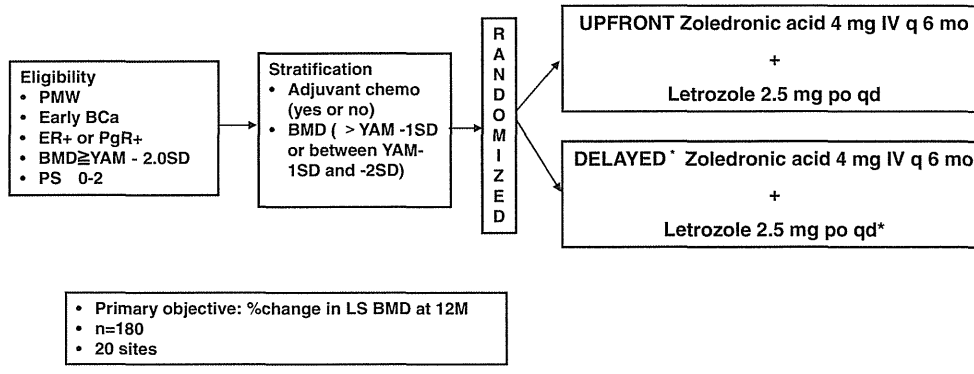

Fig. 1 Study design. *Received ZA when L_2–L_4 BMD decreased to <YAM −2.0SD or when a nontraumatic fracture occurred. *PMW* postmenopausal women, *Bca* breast cancer, *BMD* bone mineral density, *YAM* young adult mean, *Chemo* chemotherapy, *ER* estrogen receptor, *PgR* progesterone receptor

between groups; paired t test was used to compare differences within treatment groups in LS and TH BMD and serum NTx and BSAP concentrations from baseline to month 12.

The study was not powered to detect a difference in the incidence of clinical fractures or breast cancer relapse. The frequency of AEs was reported for both groups.

Results

Study population

Between May 2008 and April 2009, 204 patients were randomized in 18 Japanese centers to receive either upfront or delayed zoledronic acid. The baseline characteristics of the two groups were similar except for body mass index (BMI; Table 1).

Five patients (5.2%) and 7 patients (7.2%) in the delayed group received zoledronic acid therapy by months 6 and 12, respectively. For these patients, the mean time to initiation of zoledronic acid was 7.6 months (range 5.9–12.3 months). Of these, 4 patients were started based on the LS (L_2–L_4) BMD falling to less than YAM −2.0SD. Three patients were started because of misunderstanding of the protocol at the site level.

BMD

At month 12, the mean percent difference in BMD between the groups was 4.9% for L_1–L_4 (95% CI 3.9–5.8%; $p < 0.0001$), 5.6% for L_2–L_4 (95% CI 4.4–6.6%; $p < 0.0001$), and 4.4% for TH (95% CI 3.3–5.3%; $p < 0.0001$) (Fig. 2).

At baseline, 115 (59.3%) patients had normal LS (L_2–L_4) BMD (57 patients, 58.8% in the upfront group; 58 patients, 59.8% in the delayed group). At 12 months, a higher percentage of patients in the delayed group with normal baseline BMD developed mild to moderate osteopenia (between YAM −1.0SD and YAM −2.0SD) compared with patients in the upfront group (24.1 vs. 0%). The difference in distributions was statistically significant ($p = 0.0001$). At baseline, 79 (40.7%) patients had already had mild to moderate osteopenia at the LS (L_2–L_4) BMD (40 patients, 41.2% patients in the upfront group, and 39 patients, 40.2% patients in the delayed group). In the upfront group, BMD improved to normal (more than YAM −1.0SD) in 22.2% of patients, and there were no patients with severe osteopenia (less than YAM −2.0) at 12 months. In the delayed group, BMD improved to normal in 5.1% of the patients, but worsened to severe osteopenia in 5.1% of the patients. The difference in distributions was statistically significant ($p = 0.00435$) (Table 2). In the patients with baseline TH BMD between YAM −1.0SD and YAM −2.0SD, BMD improved to normal in 21.1% and none worsened to severe osteopenia in upfront group, but none improved to normal and 16% worsened to severe osteopenia in delayed group (Fig. 3).

Markers of Bone Turnover

In the upfront group, the levels of serum NTx decreased by 6.5% at 6 months and by 23.6% at 12 months from baseline significantly ($p = 0.0026$ and $p < 0.0001$, respectively). Serum BSAP also decreased by 33.6% at 6 months and by 39.4% at 12 months from baseline significantly ($p < 0.0001$ and $p < 0.0001$, respectively). On the other hand, in the delayed group, serum NTx and BSAP increased by 21.8% at 6 months and by 9.4% at 12 months ($p = 0.0563$ and $p = 0.2619$, respectively) and by 14.9% at 6 months and by 10.2% at 12 months ($p = 0.0291$ and $p = 0.4694$, respectively), with no significance (Fig. 4).

Fractures

At month 12, no nontraumatic clinical fracture occurred in patients receiving upfront and delayed-start zoledronic acid.

Safety

Safety analysis was evaluated in 194 cases that were treated with the investigating drugs. AEs of occurrence with 5% or more are shown in Table 3. Fever occurred significantly more in the upfront group (23.2 vs. 3.1%, $p < 0.001$). The fever is the acute phase response to bisphosphonates, and usually occurs only at the first treatment with zoledronic acid. There was no significant increase of fever with zoledronic acid at the second or the third treatment. There was no significant difference of AEs other than fever between the two groups. Arthralgia occurred in about 50% of both groups, but almost all were grade 1 and controllable with NSAIDs. Two patients withdrew from the study due to arthralgia. If the patient was diagnosed or was suspected to have osteonecrosis of the jaw (ONJ), the patients should be withdrawn from the study, but no one was diagnosed or suspected to have ONJ.

Discussion

Letrozole is a non-steroidal, reversible aromatase inhibitor similar to anastrozole, but is reported to be more effective in inhibiting aromatase and decreasing estrogen levels in vitro and in vivo [21, 22]. The randomized comparative study of letrozole and anastrozole for postmenopausal early breast cancer patients (FACE study) is ongoing [23]. On

Table 1 Basal patient characteristics

Characteristic	Upfront group	Delayed group	*p*
Patients in safety population	97	97	
Age (years)			
Mean ± SD	61.47 ± 6.80	60.45 ± 6.56	0.4052
Median (range)	60.0 (48.0–82.0)	60.0 (46.0–79.0)	
BMI			
Mean ± SD	24.26 ± 3.87	23.08 ± 3.16	0.0329
Median (range)	24.2 (15.6–43.6)	22.5 (15.6–33.3)	
ECOG PS			
0	97	97	
1	0	0	
2	0	0	
Menopausal status			
Bilateral oophorectomy	1	1	0.9787
≥55 years with cessation of menses	83	82	
Amenorrheic in women <55 years	13	14	
Bone mineral density (g/cm^2)			
Lumbar spine(L_1–L_4), mean ± SD	0.9791 ± 0.1242	0.9714 ± 0.1370	0.6854
Total hip, mean ± SD	0.8547 ± 0.1195	0.8318 ± 0.1061	0.1641
Clinical stage			
I	48	52	0.2950
IIA	31	26	
IIB	10	15	
IIIA	8	3	
Unknown	0	1	
ER status			
−	0	0	
+	97	97	
PgR status			
−	26	25	0.7088
+	69	71	
Unknown	2	1	
Nodal status			
−	74	65	0.1843
+	23	32	
Surgery			
Breast conserving	68	65	0.6389
Mastectomy	28	31	
Unknown	1	1	
Stratification factors			
Prior adjuvant chemotherapy	38	39	0.8833
Normal BMD	57	58	0.8838
Osteopenia BMD	40	39	

Normal BMD: less than YAM −1.0SD

Osteopenia BMD: between YAM −1SD and YAM −2SD

the other hand, letrozole may cause aromatase inhibitor-associated bone loss (AIBL) more severely with stronger inhibitory activity, but bone marker changes, severity of bone loss or increase of fracture rate seem similar to anastrozole in clinical studies so far [24, 25].

In Japanese patients, AIBL may be less severe from some studies. Yoneda et al. [18] reported that there were no significant changes in BMD and bone metabolic markers in Japanese women treated with anastrozole for 1 year. Okisiro et al. [26] also showed that bone loss of Japanese women induced by anastrozole was less compared that of ATAC bone study (1.3 vs. 2.2% at 1 year and 2.8 vs. 4.0% at 2 years). In the Japanese subgroup bone study of TEAM, BMDs of patients treated with tamoxifen versus

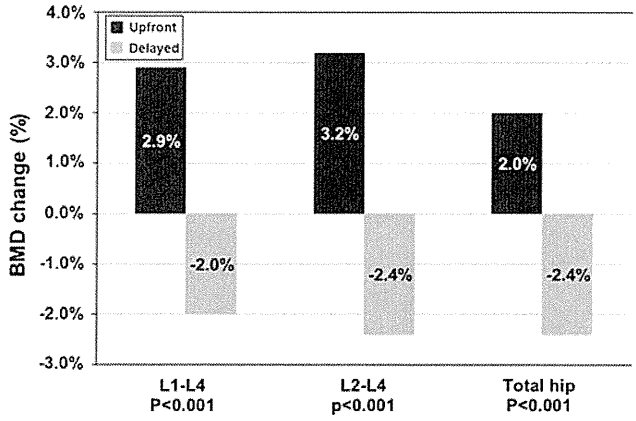

Fig. 2 Mean percent change in BMD of LS (L_1–L_4 and L_2–L_4) and TH at 12 month. p value was calculated by t test

Table 2 LS BMD measurements at month 12

Baseline and month 12 BMD	Upfront group		Delayed group	
	No.	%	No.	%
Normal baseline BMD, month 12 BMD	54		58	
Normal	54	100	44	75.9
Mild osteopenia	0		14	24.1
Osteopenia at baseline BMD, month 12 BMD	36		39	
Normal	8	22.2	2	5.1
Mild osteopenia	28	77.8	35	89.7
Severe osteopenia	0		2	5.1

Normal BMD: **YAM −1SD

Mild osteopenia BMD: between YAM −1SD and YAM −2SD

Severe osteopenia BMD: <YAM −2SD

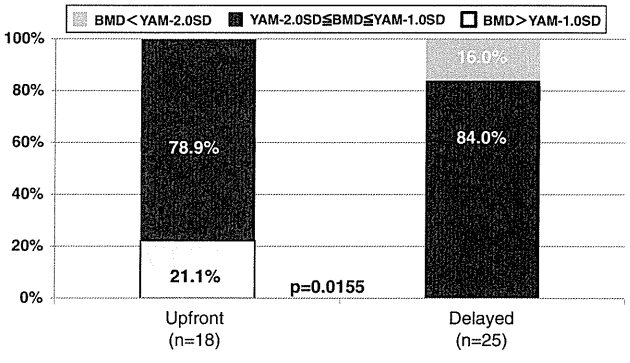

Fig. 3 Shift in TH BMD distribution at 12 months in patients with baseline BMD between YAM −2SD and YAM −1SD. p value was calculated by χ^2 test

exemestane after 1 and 2 years were 88.1 and 87.8% versus 87.5 and 86.8%, although bone metabolic markers (urine NTx and BSAP) were significantly high in exemestane

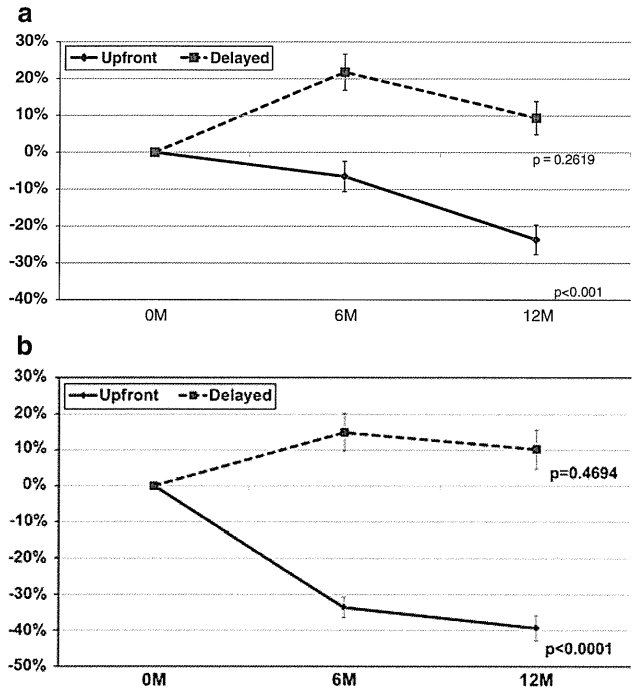

Fig. 4 Mean % change in serum **a** NTx and **b** BSAP from baseline. p value was calculated by t test

Table 3 AEs >5% of patients

AE	Upfront ($N = 95$)	Delayed ($N = 97$)	Fisher, p
Fever	22 (23.2)	3 (3.1)	<0.001
Fatigue	9 (9.6)	11 (11.3)	0.805
Hot flashes	13 (13.7)	9 (9.3)	0.397
Sweating	5 (5.3)	3 (3.1)	0.580
Arthralgia	49 (51.6)	47 (48.5)	0.925
Myalgia	6 (6.4)	6 (6.2)	0.602
Nausea	5 (5.3)	2 (2.1)	0.324
Pruritus	5 (5.3)	3 (3.1)	0.276
Rash	5 (5.3)	2 (2.1)	0.324

No cases of ONJ have been reported

group compared with tamoxifen group [19]. In the phase III study, comparing tamoxifen for 5 years versus switch from tamoxifen for 1–4 years to anastrozole for 1–4 years in Japanese postmenopausal breast cancer patients (N-SAS BC03), fracture rate was not significantly different between two groups (tamoxifen 2.6%, tamoxifen to anastrozole 1.4%) [20]. AIBL has not been proved clinically significant in Japan yet. This is the first study that prospectively investigated AIBL with BMD as the primary endpoint in multi-institutions of Japan.

Bisphosphonates have been reported to be effective for inhibiting AIBL. Some studies have shown that those oral bisphosphonates prevent aromatase inhibitor-induced bone

loss [11, 27]. Weekly 35 mg risedronate treatment for 2 years improved BMD by 4.0% at LS and 2.9% at femoral bone in anastrozole-treated breast cancer patients. Monthly 150 mg oral ibandronate treatment for 12 months also improved BMD by 5.45% at LS and 3.3% at femoral bone in anastrozole-treated breast cancer patients with osteopenia. For letrozole-associated bone loss, treatments with zoledronic acid 4 mg every 6 months inhibit bone loss at 1 year in three randomized studies in western countries, Z-FAST [16], ZO-FAST [17], and E-ZO-FAST [28].

To investigate whether letrozole causes bone loss in Japanese women at the same level as in Caucasian women and whether zoledronic acid can inhibit AIBL similarly, we performed prospective randomized study to compare changes of L_1–L_4 BMD in upfront group who are treated by zoledronic acid every 6 months or delayed group who are treated with zoledronic acid after occurrence of bone loss in Japanese postmenopausal breast cancer patients treated with adjuvant letrozole therapy, as the same way as those in Z-FAST or ZO-FAST study, and compare those data.

In the western countries, WHO reported the diagnostic categories of osteoporosis at 2004 [29], which use *T* score to evaluate BMD. In Japan, BMD was evaluated as percentage of YAM of L_2–L_4 according to diagnostic guideline for primary osteoporosis of Japanese Society of Bone Mineral Metabolism [30]. In this study, eligible patients had BMD of more than YAM −2.0SD in L_2–L_4, although eligible patients had BMD of T score −2.0SD in L_1–L_4 and TH.

In the delayed group, BMDs after 12 months of L_1–L_4, L_2–L_4, and TH decreased by 2.0, 2.4, and 2.4% compared with baseline. These data are comparable to BMD decrease of L_1–L_4 and TH (3.5 and 2.4%) in the delayed group of ZO-FAST study, so letrozole-induced bone loss is almost similar to Caucasian women in Japanese women. Furthermore, BMD worsened to mild osteopenia in 25% of patients with normal baseline BMD, and to severe osteopenia in 5.1% of the patients with mild baseline osteopenia at 12 months. In Z-FAST study, 12.6% of patients with normal baseline BMD changed to mild osteopenia, and 14.8% of patient with mild baseline osteopenia changed to severe osteopenia at 12 months. Our data about transition are also comparable to those of western country studies. Therefore, AIBL is clinically significant also in Japan.

Upfront treatment with zoledronic acid 4 mg every 6 months increased BMD of L_1–L_4, L_2–L_4, and TH at 12 months by 2.9, 3.2, and 2.0% from baseline. Differences between upfront group and delayed group were significant ($p < 0.001$). The improvement of BMD (4.9, 5.6, and 4.4%) with zoledronic acid was also comparable to ZO-FAST study (5.7% at L_1–L_4, and 3.6% at TH). So, zoledronic acid is also effective for preventing AIBL in Japanese women.

Bone metabolic markers, serum NTx and BSAP concentrations decreased significantly from baseline in upfront group, which suggested that zoledronic acid suppresses the letrozole-associated bone resorption rapidly and maintains normal bone metabolism at least for 12 months. The rates of decrease were also comparable to those of Z-FAST study. On the other hand, both serum NTx and BSAP tended to increase from the baseline in the delayed group and suggested letrozole-induced bone resorption, although those were not significant. The number of actual measurement of serum bone marker in the delayed group was 60% of the scheduled measurement, and it might cause the insignificance.

Decrease of BMD is a strong surrogate for fracture events in postmenopausal women, although fracture risk is influenced by many factors such as age, body weight, smoking, prior fracture, exercise. In BIG1-98 study, fracture rate in the first year of letrozole-treated patients was 2.2% [31, 32]. In out study, adjuvant letrozole therapy decreased BMD of LS and TH similarly to western studies, but no non-traumatic fracture occurred at 12 months. We will investigate occurrence of fracture after 2, 3, and 5 years.

In the combined analysis of Z-FAST and ZO-FAST study, significant decrease of breast cancer relapse was shown in the upfront group [33]. Recently, the results of the adjuvant randomized phase IIII study of zoledronic acid (AZURE) were reported [34]. Adjuvant zoledronic acid (4 mg div monthly for 6 months, 3-monthly for 1.5 years, then 6-monthly for 3 years) with standard therapy decreased breast cancer relapse in postmenopausal patients. In our study, only one patient in the upfront group had a relapse of breast cancer. We will also investigate occurrence of relapse at after 2, 3, and 5 years.

This study is ongoing, and will continue treatment and follow-up for 5 years. At the 12-month data, upfront 4 mg zoledronic acid treatment every 6 months was effective for inhibition of bone loss with adjuvant letrozole treatment. Especially, the patients with bone loss (between YAM −1.0SD and YAM −2.0SD) at the start of aromatase inhibitor therapy have high risk of osteoporosis without appropriate therapy such as bisphosphonates.

In conclusion, AIBL occurs in Japanese women just the same way with Caucasian women, and upfront zoledronic acid therapy prevented bone loss in postmenopausal Japanese women who were receiving adjuvant letrozole, confirming the Z-/ZO-FAST study results in western populations.

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BJU INTERNATIONAL

Clinical efficacy and prognostic factors for overall survival in Japanese patients with metastatic renal cell cancer treated with sunitinib

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Study Type – Therapy (case series)
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What's known on the subject? and What does the study add?
A randomized prospective phase III clinical trial for systemic treatment-naïve metastatic renal cell cancer (RCC) patients demonstrated the superiority of sunitinib over interferon with an acceptable safety profile. However, a commonly asked question is whether patients with RCC in clinical trials are representative of those with this disease being seen in ordinary clinical practice.

To our knowledge, this is the first report of sunitinib for the Japanese patients with metastatic RCC in ordinary clinical practice. The estimated median PFS and OS in this study were 9.3 and 32.2 months, respectively. The application of the MSKCC model distinctly separated OS curves ($P<0.001$), suggesting that MSKCC prognostic factors might be still valid to predict survival in metastatic RCC in the era of molecular targeted therapy.

OBJECTIVES

- To report the treatment efficacy and safety profile of sunitinib for patients with metastatic renal cell carcinoma (RCC) in ordinary clinical practice.
- In addition, to investigate the prognostic clinicopathological factors in these patients.

PATIENTS AND METHODS

- The present study consisted of native Japanese patients with metastatic RCC, comprising 29 pretreated and 34 systemic treatment-naïve patients.
- Univariate and multivariate analyses were performed by the log-rank test and the Cox proportional hazards model, respectively.

RESULTS

- Estimated median progression-free survival and overall survival (OS) were 9.3 months (95% confidence interval, CI, 5.0–13.7) and 32.2 months (95% CI, 24.4–40.0), respectively.
- Among the patients pretreated before sunitinib, two patients were treated with initialized systemic therapy with sorafenib and the remaining 27 were initialized with interferon-α.
- The OS from the initial systemic therapy of the patients in pretreated groups was 79.6 months (95% CI, 14.6–144.5).
- The application of the Memorial Sloan-Kettering Cancer Center model distinctly separated the OS curves ($P<0.001$).
- The most common grade 3 adverse events were fatigue (53%), thrombocytopaenia (48%), hand-foot syndrome (16%), anaemia (20%), hypertension (10%) and leucopaenia (9%), although these events were manageable and reversible.

CONCLUSIONS

- Sunitinib has a favourable efficacy/safety profile for Japanese metastatic RCC patients in clinical practice.
- The estimated median OS was >2 years with acceptable tolerability.
- The median OS from the initial systemic therapy of the pretreated patients was >6 years.
- Memorial Sloan-Kettering Cancer Center prognostic factors still appear to be valid for predicting survival in metastatic RCC in the era of molecular targeted therapy.

KEYWORDS

MSKCC score, outcome, prognostic factor, renal cell cancer, sunitinib

INTRODUCTION

Sunitinib is an orally administered, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1–3 and platelet-derived growth factor receptors α and β [1,2]. A randomized, prospective phase III clinical trial for systemic treatment-naïve metastatic RCC patients showed the superiority of sunitinib over interferon with respect to objective response rate (ORR) (31% vs 6%), progression-free survival (PFS) (11 vs 5 month) and overall survival (OS) (26.4 vs 21.8 months), with an acceptable safety profile [3,4]. These results indicate an improved prognosis in patients with RCC in the era of targeted therapy.

The first Japanese phase II study of single-agent sunitinib, which was conducted in 51 patients with metastatic RCC, also showed efficacy and tolerability comparable to that observed in Western patients [5]. In that study, the ORR was 52.0% in treatment-naïve patients, 53.8% among cytokine-pretreated patients and 52.9% in the overall population [5]. As a result of these findings, the multinational approvals of sunitinib for treatment of first- and second-line advanced RCC now include Japan.

However, a commonly asked question is whether patients with RCC in clinical trials are representative of those with this disease who are seen in ordinary clinical practice. Many patients with RCC do not meet the inclusion criteria, particularly those with a poorer prognosis. Patients with a poor performance status (PS), brain metastasis or other clinical parameters predicting shorter survival are often excluded from clinical trials. In the present study, we report the treatment efficacy and safety profile of sunitinib for patients with metastatic RCC in ordinary clinical practice. In addition, we also investigated the prognostic clinicopathological factors associated with OS in this population.

PATIENTS AND METHODS

PATIENT POPULATION

The present study consisted of native Japanese patients with metastatic RCC. The study group comprised 29 patients pretreated before sunitinib and 34 systemic treatment-naïve patients, who were all undergoing treatment at the Akita University Medical Center or the Cancer Institute Hospital, Japanese Foundation for Cancer Research, from March 2006 until January 2011. The patients included in the retrospective study were not consecutive. In this period, patients with metastatic renal cell cancer were treated by sunitinib or interferon-α as an initial treatment and sunitinib or sorafenib as a secondary treatment, fundamentally. All RCC patients were diagnosed on the basis of histological analysis of specimens obtained by radical nephrectomy or ultrasonographically-guided needle biopsy.

TREATMENT AND ASSESSMENT

Each patient signed a protocol-specific informed consent, approved by an institutional review board, in accordance with national and institutional guidelines. Sunitinib was administered orally at a dose of 50 mg daily, for 4 weeks followed by a 2-week rest period. Sunitinib was discontinued in the case of grade 3 or 4 toxicity and was re-administrated when toxicity was ≤grade 1. In the case of grade 3 non-haematological toxicity or grade 4 haematological toxicity, a dose reduction of sunitinib (to 37.5 mg and then to 25 mg) was allowed. The response was assessed by CT scans performed at least every two cycles of treatment, in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [6]. Safety and tolerability were assessed at regular intervals with adverse event monitoring using National Cancer Center Common Toxicity Criteria for Adverse Events, version 3.0, to document adverse events and classify severity; haematology and biochemistry; body weight; vital signs; and Eastern Cooperative Oncology Group (ECOG) PS.

STATISTICAL ANALYSIS

OS and PFS were measured from the initial administration of sunitinib until death from any cause, and from the date of initial administration of sunitinib until objective tumour progression or death, respectively. Time-to-event distributions were estimated using Kaplan–Meier curves. Univariate and multivariate analyses were performed by the log-rank test and the Cox proportional hazards model, respectively, aiming to assess the relationship between OS and the laboratory, as well as clinical variables. The laboratory variables included haemoglobin (Hb; male: <13 g/dL vs ≥13 g/dL; female: <11.5 g/dL vs ≥11.5 g/dL); neutrophil count (≤6600/μL vs >6600/μL); platelet count (≤4.5×10^5/μL vs >4.5×10^5/μL); corrected calcium (≤10 mg/dL vs >10 mg/dL) and lactate dehydrogenase (LDH; ≤1.5×230 IU/dL vs >1.5×230 IU/dL). The clinical variables included ECOG PS (≤1 vs >1); time from diagnosis of RCC to systemic therapy initiation (<12 months vs ≥12 months); time from diagnosis to sunitinib initiation (<12 months vs ≥12 months); history of nephrectomy (no vs yes); number of metastatic sites (1 vs ≥1); presence or absence of lung, bone, lymph node and brain metastasis (yes vs no); tumour grade (I, II vs III); clear cell histology (clear cell or no clear cell histology); and the presence or absence of sarcomatoid component (without sarcomatoid component vs with sarcomatoid component). The corrected serum calcium level was calculated using Payne's formula [7]. SPSS software was used for statistical analysis (SPSS for Windows, version 17.0, SPSS Inc., Chicago, IL, USA).

RESULTS

PATIENT CHARACTERISTICS

The characteristics of the patients treated with sunitinib are shown in Table 1. Among the patients pretreated before sunitinib, two patients were initialized with systemic therapy with sorafenib because the approval of sorafenib had been given 3 months before that of sunitinib in Japan. The remaining 27 patients were initialized with interferon-α. The median (interquartile range) follow-up from the initial systemic therapy and sunitinib start was 17.3 (8.0–40.1) months and 7.7 (3.3–16.4) months, respectively. Overall, 19 (30%) patients showed a partial response and 32 (51%) patients showed stable disease longer than 3 months by RECIST criteria, indicating that 81% of the patients experienced a clinical benefit from sunitinib. Progression within 3 months was observed in 12 (19%) patients, and none experienced an early treatment failure before the initial assessment.

TABLE 1 Patient characteristics

Variable	Value
Age (years), median (range)	62 (27–81)
Sex, *n* (%)	
Male	50 (79)
Female	13 (21)
Diagnosis to systemic therapy, *n* (%)	
1 year	16 (25)
>1 year	47 (75)
Diagnosis to sunitinib, *n* (%)	
≤1 year	30 (48)
>1 year	33 (52)
Previous systemic therapy, *n* (%)	
Yes	29 (46)
No	34 (54)
Nephrectomy, *n* (%)	
Done	49 (78)
None	14 (22)
Number of metastatic sites, *n* (%)	
1	31 (49)
<1	32 (51)
Metastatic sites, *n* (%)	
Lung	43 (68)
Liver	16 (25)
Bone	19 (30)
Lymph node	24 (38)
Brain	5 (8)
Histological subtype, *n* (%)	
Clear cell type	51 (81)
Papillary type	6 (10)
Chromophobe type	2 (3)
Others	4 (6)

PFS AND OS

Estimated median PFS and OS were 9.3 months (95% CI, 5.0–13.7) and 32.2 months (95% CI, 24.4–40.0), respectively. Estimated 12-month PFS and 18-month OS rates were 47.8% and 53.7%, respectively. During follow-up, 28 (44%) patients died from RCC. In addition, we investigated the OS from the initial systemic therapy given to the patients in pretreated groups, and their median OS was 79.6 months (95% CI, 14.6–144.5).

PROGNOSTIC FACTORS ASSOCIATED WITH OS PERIOD

Finally, we investigated the prognostic factors associated with overall survival time. Univariate analysis showed that the various pretreatment factors were associated with worse OS (Table 2). All the factors in a

TABLE 2 Univariate analysis of factors associated with overall survival

Category	*N*	Median OS	95% CI	*P*
ECOG PS				
0–1	52	35.8	12.5–44.2	
≤2	11	6.03	2.8–9.2	0.001
Haemoglobin				
Normal	26	Not reached		
Anaemia	37	9.8	5.1–14.6	0.002
Calcium				
>10 mg/dL	56	35.0	26.7–43.3	
≤10 mg/dL	7	7.0	0.0–15.2	0.008
Lactate dehydrogenase				
≥1.5 × ULN	51	36.0	27.6–44.4	
<1.5 × ULN	12	2.3	0–8.2	<0.001
Dx to systemic Tx				
≤1 year	16	Not reached		
>1 year	47	12.5	3.2–21.8	0.037
Neutrophil count				
≥ULN	55	34.8	26.4–43.2	
<ULN	8	4.9	0–10.6	0.054
Platelet count				
≥ULN	59	33.9	25.8–42.1	
<ULN	4	3.4	1.9–4.8	0.051
Dx to sunitinib				
≤1 year	30	38.2	12.3–21.3	
>1 year	33	10.6	6.5–14.7	0.106
Previous systemic therapy				
Yes	29	Not reached		
No	34	28.8	19.8–37.8	0.719
Nephrectomy				
Done	49	36.1	27.4–44.7	
None	14	10.3	5.8–15.1	0.039
Number of metastatic sites				
1	31	38.5	31.4–45.6	
<1	32	9.8	4.6–15.0	0.002
Lung metastasis				
Yes	43	37.0	27.3–46.8	
No	20	31.2	22.5–40.0	0.188
Liver metastasis				
Yes	16	7.0	4.0–9.9	
No	47	Not reached		0.082
Bone metastasis				
Yes	19	11.6	7.5–15.9	
No	44	33.4	24.5–42.3	0.328
Lymph node metastasis				
Yes	24	10.6	7.7–13.5	
No	39	35.5	26.2–44.7	0.171
Brain metastasis				
Yes	5	6.4	0.0–13.1	
No	58	35.3	27.2–43.4	0.001
Grade				
1, 2	32	Not reached		
3	19	10.3	8.2–12.3	0.158
Histology				
Clear cell	51	33.3	24.9–41.8	
Non-clear cell	12	16.9	2.9–17.6	0.961
Sarcomatoid				
Without sarcomatoid	53	35.3	26.9–43.8	
With sarcomatoid	10	7.0	7.0–7.2	0.014

ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; Dx, diagnosis; Tx, treatment; ULN, upper limit of normal range.