Efficacy and Safety of Sunitinib in Elderly Patients with Advanced Renal Cell Carcinoma at a University Hospital in Japan: Before Immuno-Oncology Therapy Era

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Abstract

Introduction: The efficacy and safety of sunitinib in elderly patients with advanced renal cell carcinoma (RCC) remains poorly documented.

Methods: We assessed the efficacy and safety of sunitinib in first-line treatment of advanced RCC in the aged by reviewing the medical records of patients at Jichi Medical University Hospital, Japan. The patients were stratified into age < 75 (n = 38) and ≥ 75 (n = 9) years groups.

Results: Median progression-free survival in younger and older patients was comparable, at 7.3 vs. 6.7 months, respectively (HR, 1.101; 95% CI: 0.399-3.039; p = 0.8532). Median overall survival was also comparable, at 19.2 vs. 11.8 months (HR, 0.775; 95% CI: 0.349-1.719; p = 0.5299). Younger and older patients did not significantly differ in the frequency of any grade and grade 3 or more adverse events, or in the incidence of patients with grade 3 or more adverse events.

Conclusions: Treatment with sunitinib is effective and safe in elderly patients with advanced RCC although the limited sample size for older group can cause weak statistical power and only patients with no severe comorbidities were selected.

Keywords
Elderly, Renal cell carcinoma, Sunitinib, Efficacy, Safety

Introduction

Japan is a front-line country in the coming super-aging society. As with all cancers in the elderly [1], the frequency of renal cell carcinoma (RCC) is also increasing in Japan [2]. While clinical encounters with elderly patients with advanced RCC increase, these patients are only infrequently entered into clinical trials [3], and efficacy and safety data in this age range are scarce.

Sunitinib is an oral tyrosine-kinase inhibitor (TKI) of vascular endothelial receptor and other receptors which significantly prolongs the progression-free survival (PFS) [4-6] and overall survival (OS) [5,6] of patients with metastatic RCC. Sunitinib also induces a range of adverse events, however, including symptomatic and laboratory toxicities; the former include hypertension, fatigue, diarrhea, nausea, vomiting, stomatitis, hand-foot syndrome and hypothyroidism while the latter include leukopenia, anemia, thrombocytopenia and increased creatinine [4-6]. Despite this apparently large number of treatment-related adverse events, prolonged treatment with sunitinib is not associated with new types or increased severity of treatment-related adverse events. Apart from hypothyroidism, toxicity is not cumulative [7]. In an expanded access trial of sunitinib, median PFS among patients aged over 65 years was 10.1 months compared to 8.9 months for the whole population. Except for fatigue, patients aged over 65 years appear to have experienced no worse grade 3-4 non-hematological adverse events than the whole population of patients [5].

In general, while people aged over 65 years are con-
Considered elderly, age-related physiological changes occur predominantly in those between 70 and 75 years. Physiological function decreases as age progresses beyond 75 years [8,9], yet few papers define a cut-off point for older cancer patients of 75 years. Our present study is the first to evaluate the efficacy and safety of first-line anticancer

| Variable | Age < 75 years (n=38) | Age ≥ 75 years (n=9) | p values |
|----------|-----------------------|----------------------|----------|
| Median (range) age, years | 62(37-74) | 77(75-84) | < 0.0001 |
| Male/female, % | 76/24 | 90/10 | 0.4073 |
| Hypertension, n(%) | 20(53) | 6(67) | 0.4463 |
| Diabetes mellitus, n(%) | 8(22) | 2(22) | 0.9386 |
| Smoking history, n(%) | 21(55) | 5(56) | 0.8467 |
| Prior nephrectomy, n(%) | 15(39) | 4(44) | 0.7847 |
| ECOG PS, n(%) | | | |
| 0 | 21(55) | 3(33) | 0.2073 |
| 1 | 9(24) | 5(56) | 0.2161 |
| ≥2 | 6(16) | 1(11) | |
| Missing (unknown) | 2(5) | 0(0) | |
| Risk factors based on MSKCC data, n(%) | | | |
| 0 (favorable) | 4(11) | 0(0) | |
| 1-2 (intermediate) | 21(55) | 8(89) | 0.1483* |
| ≥3(poor) | 11(29) | 1(11) | |
| missing | 2(5) | 0(0) | |
| Common site of metastasis, n(%) | | | |
| Lung | 21 (55) | 6 (67) | 0.5338 |
| Bone | 11 (29) | 3 (33) | 0.7959 |
| Lymph nodes | 10 (26) | 3 (33) | 0.6722 |
| Histology, n(%) | | | |
| Clear cell | 19(50) | 6(67) | 0.4807 |
| Others | 3(8) | 0(0) | 0.3384 |
| Missing (untraced or unknown) | 16(42) | 3(33) | |
| Initial doses of sunitinib, n(%) | | | |
| 50 mg | | | |
| 4 weeks on, 2 weeks off | 27(70) | 5(56) | |
| 2 weeks on, 1 weeks off | 3(8) | 0(0) | |
| 37.5 mg | | | |
| 4 weeks on, 2 weeks off | 6(16) | 3(33) | 0.1483* |
| 2 weeks on, 1 weeks off | 0(0) | 1(11) | |
| 25 mg | | | |
| 4 weeks on, 2 weeks off | 1(3) | 0(0) | |
| 2 weeks on, 1 weeks off | 1(3) | 0(0) | |
| Relative dose intensity, % | | | |
| median | 75.0 | 68.8 | 0.7559 |
| mean±SD | 72.5±19.4 | 70.4±15.9 | 0.8105 |
| Clinical outcome of sunitinib treatment, n(%) | | | |
| Continuing sunitinib | 3(8) | 0(0) | 0.3837 |
| Discontinuing sunitinib | 35(92) | 9(100) | |
| Reason for discontinuation (n=42) | | | |
| Lack of efficacy | 17(44) | 6(67) | |
| Progressive disease | 16(41) | 5(56) | |
| Stable disease with increasing tendency | 1(3) | 0(0) | |
| Death | 0(0) | 1(11) | 0.5019 |
| Adverse events | 15(40) | 3(33) | |
| Others | 3(8) | 0(0) | |

All statistical analysis was carried out except for missing data. Mean and median relative dose intensity (%) was calculated during the first 6 weeks of treatment. *50mg vs ≤37.5mg; p= 0.1787

**Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; SD, standard deviation

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treatment with sunitinib stratified by age 75 years.

Materials and Methods

The study was conducted as a retrospective analysis of 47 patients with advanced RCC treated with sunitinib in the first-line setting, except for use in neoadjuvant or presurgical therapy, between May 2008 and August 2016 at the Department of Urology, Jichi Medical University Hospital. The observation period for each patient extended from the start of sunitinib treatment until disease progression, death or August 2016, whichever occurred first.

Materials and Methods

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Data for age, sex, hypertension, diabetes mellitus, smoking history, prior nephrectomy, Eastern Cooperative Oncology Group performance status, Memorial Sloan-Kettering Cancer Center data, common site of metastasis, histology, treatment dose and schedule of sunitinib, relative dose intensity, PFS, OS and adverse events were obtained from medical records. Protocols were approved by the Institutional Research Review Boards of Jichi Medical University with an opt-out system (No. A14-129). Toxic effects were registered according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Response was assessed by the treating physician according to the Response Evaluation Criteria in Solid Tumor (RECIST) 1.0 criteria.

Patients were divided into age groups of <75 and ≥ 75 years. Categorical variables were expressed as frequencies and percentages, and differences were compared using Pearson’s chi-square test. PFS and OS curves were depicted using the Kaplan-Meier method and compared with the log-rank test. All P values presented are two-sided. Statistical significance was calculated using StatView ver. 5 (Abacus Concepts, CA, USA), with P values of <0.05 considered to indicate statistical significance.

Results

The study included 47 patients with advanced RCC who were treated with sunitinib as first-line treatment, except for use in neoadjuvant or presurgical therapy. There were 38 and 9 patients aged <75 and ≥ 75 years, respectively. Baseline characteristics of the patients and data on treatment exposure to sunitinib are shown in Table 1. Baseline characteristics between the two groups were similar. Among the two groups, 71% of patients aged <75 were administered sunitinib at 50 mg/day orally in a 4 weeks on, 2 weeks off regimen, as were 56% of those aged ≥ 75 years. In contrast, starting dose of sunitinib did not significantly differ between the two age groups even if 50 mg vs. ≤ 37.5 mg daily. Further, mean and median relative dose intensity during the first 6 weeks of treatment was similar between the two groups. The median follow-up was 16.9 months (range, 0.6-80.9 months). Three patients aged <75 continued sunitinib treatment. The most common reasons for discontinuation were progressive disease and adverse events, with no significant difference in reasons between the two groups. Other reasons for discontinuation included complete response (n = 1), cost concerns (n = 1) and patient refusal (n = 1). Twenty-two patients (58%) aged <75 and 6 Patients (66%) aged ≥ 75 years received second-line treatment. The former consisted of axitinib (n = 8), everolimus (n = 7), sorafenib (n = 4), temsirolimus (n = 2) and

Figure 1: Kaplan-Meier curves of progression-free survival (A) and overall survival (B) in sunitinib-treated patients by age (<75 vs. ≥ 75 years).

There were no significant differences in PFS or OS between the <75 and ≥75-year groups.
cytokine (n = 1) and the latter consisted of axitinib (n = 2), everolimus (n = 3) and sorafenib (n = 1). The next treatments did not incorporate anti-programmed death 1 therapy during the observation period.

We compared the difference in PFS and OS in the two groups. Median PFS in the younger and older patients was comparable, at 7.3 vs. 6.7 months, respectively (HR, 1.101; 95% CI: 0.399-3.039; p = 0.8532), as was median OS, at 19.2 vs. 11.8 months (HR, 0.775; 95% CI: 0.349-1.719; p = 0.5299), with neither of these differences being significant (Figure 1). The best response of sunitinib treatment in patients aged < 75 was composed of CR (n = 1), PR (n = 1), SD (n = 30) and PD (n = 6), as was SD (n = 9) in those aged ≥ 75 years.

Table 2 shows adverse events occurring in at least 20% of patients or at grade 3 or 4. Symptomatic adverse events with a frequency of more than 30% were nausea, fever, fatigue, anorexia, hand-foot syndrome, hypertension, and stomatitis. There was no significant difference in adverse events of any grade or of grade 3 between the two groups, except for a significant difference in the incidence of grade 3 diarrhea, albeit that this occurred in only one patient aged ≥ 75 years. Abnormal laboratory data with a frequency of more than 40% were AST increased, ALP increased, platelet count decreased, ALT increased, hypothyroidism, creatinine increased, neutrophil count decreased, leukocyte count decreased, hypotremia, blood urea nitrogen increased and hypocalcemia. These showed no significant difference for any grade

Table 2: Adverse events in sunitinib-treated patients classified by age

| Adverse Event                              | Variable | Age < 75 years (n=38) | Age ≥ 75 years (n=9) | p values |
|--------------------------------------------|----------|-----------------------|---------------------|----------|
|                                            |          | All grade            | ≥ Grade 3           | All grade | ≥ Grade 3 |
| Symptoms, n (%)                            |          |                      |                     |          |
| Nausea                                     |          | 20(53)                | 0(0)                | 3(33)     | 0(0)      | 0.2977 - |
| Fever                                      |          | 16(42)                | 0(0)                | 3(33)     | 0(0)      | 0.6297 - |
| Fatigue                                    |          | 15(39)                | 0(0)                | 3(33)     | 0(0)      | 0.7333 - |
| Anorexia                                    |          | 15(39)                | 2(5)                | 3(33)     | 2(22)     | 0.7333 0.1011 |
| Hand-foot syndrome                         |          | 14(37)                | 3(8)                | 4(44)     | 2(22)     | 0.6731 0.216 |
| Hypertension (de novo)                     |          | 14(37)                | 2(5)                | 4(44)     | 0(0)      | 0.6731 0.4818 |
| Stomatitis                                 |          | 13(34)                | 2(5)                | 3(33)     | 1(11)     | 0.9602 0.5187 |
| Diarrhea                                   |          | 10(26)                | 0(0)                | 3(33)     | 1(11)     | 0.6722 0.0378 |
| Peripheral edema                           |          | 6(16)                 | 0(0)                | 2(22)     | 0(0)      | 0.6443 - |
| Gastrointestinal hemorrhage                |          | 5(13)                 | 1(3)                | 2(22)     | 0(0)      | 0.4922 0.6228 |
| Abnormal laboratory data, n (%)            |          |                      |                     |          |
| AST increased                              |          | 31(82)                | 2(5)                | 8(89)     | 0(0)      | 0.5998 0.4818 |
| ALP increased                              |          | 25(66)                | 1(3)                | 6(67)     | 0(0)      | 0.9602 0.6228 |
| Platelet count decreased                   |          | 24(63)                | 14(37)              | 7(78)     | 3(33)     | 0.4053 0.8438 |
| ALT increased                              |          | 22(58)                | 3(8)                | 6(67)     | 0(0)      | 0.6297 0.3837 |
| Hypothyroidism*                            |          | 21(55)                | 2(5)                | 2(22)     | 0(0)      | 0.0746 0.4818 |
| Creatinine increased                       |          | 20(53)                | 1(3)                | 4(44)     | 0(0)      | 0.8349 0.6382 |
| Neutrophil count decreased                 |          | 19(50)                | 10(26)              | 6(67)     | 3(33)     | 0.3876 0.6722 |
| Leukocyte count decreased                  |          | 17(45)                | 11(29)              | 6(67)     | 3(33)     | 0.2367 0.7959 |
| Hyponatremia                               |          | 17(45)                | 4(11)               | 4(44)     | 0(0)      | 0.9354 0.3019 |
| Blood urea nitrogen increased              |          | 16(42)                | 1(3)                | 5(56)     | 0(0)      | 0.506 0.618 |
| Hypocalcemia                               |          | 15(39)                | 1(3)                | 4(44)     | 0(0)      | 0.7847 0.6228 |
| Hypophosphatemia                           |          | 14(37)                | 4(11)               | 2(22)     | 0(0)      | 0.4053 0.3089 |
| Hyperkalemia                               |          | 13(34)                | 0(0)                | 3(33)     | 0(0)      | 0.9602 - |
| Gamma-GTP increased                        |          | 12(32)                | 2(5)                | 2(22)     | 0(0)      | 0.581 0.4818 |
| Serum amylose increased                    |          | 12(32)                | 3(8)                | 2(22)     | 0(0)      | 0.581 0.3837 |
| Hyperuricemia                              |          | 12(32)                | 0(0)                | 2(22)     | 0(0)      | 0.7132 - |
| Hypercalcemia                              |          | 9(24)                 | 0(0)                | 1(11)     | 0(0)      | 0.4073 - |
| Hypokalemia                                |          | 8(21)                 | 1(3)                | 1(11)     | 0(0)      | 0.4955 0.6228 |
| Lipase Increased                           |          | 6(16)                 | 3(8)                | 2(22)     | 1(11)     | 0.6443 0.7559 |
| Total bilirubin increased                  |          | 6(16)                 | 0(0)                | 2(22)     | 0(0)      | 0.6443 - |

Graded according to CTCAEv3.0, and occurring in at least 20% of patients, or including patients with grade 3 or 4 adverse events.

*: Hypothyroidism consists of thyroid hormone decreased and thyroid-stimulating hormone increased, and most patients received medication before symptom appearance.

Abbreviations: AST: aspartate aminotransferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase; GTP: glutamyl transpeptidase
or for grade 3 between the two groups. Seven patients experienced grade 4 adverse events (data not shown), of whom six were < 75 years. These included platelet count decreased (n = 5), neutrophil count decreased (n = 1), leukocyte count decreased (n = 1), lipase increased (n = 2) and hypophosphatemia (n = 1); of these, the three former adverse events occurred in one patient aged < 75 years. Table 3 reports the incidence grade 3 or more adverse events in patients aged < 75 and ≥ 75 years were comparable although the limited sample size for older group can cause weak statistical power.

Sunitinib, an oral tyrosine-kinase inhibitor (TKI) of vascular endothelial receptor and other receptors, is recommended in various guidelines as first-line treatment of metastatic or advanced RCC. In an expanded access trial, 32% of 4371 patients who received sunitinib were 65 years or older. Median PFS, OS and frequencies of adverse events in patients aged < 75 and ≥ 75 years were comparable although the limited sample size for older group can cause weak statistical power.

The main finding of this study is that treatment with sunitinib was effective and safe in elderly patients with advanced RCC in a university hospital in Japan. Median PFS, OS and frequencies and incidences of adverse events in patients aged < 75 and ≥ 75 years were comparable although the limited sample size for older group can cause weak statistical power.

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In the present study, the efficacy of sunitinib treatment was similar between the two age groups, although mean PFS and OS were somewhat shorter than in these previous reports due to the lower frequency of prior nephrectomy and low incidence of patients with a favorable MSKCC risk profile. Moreover, among reasons for moving to next treatment, progressive disease and adverse events also occurred with increasing frequency in a post-marketing study which collected sunitinib safety and efficacy data in 1689 Japanese patients with advanced RCC [18]. Among adverse events, the frequency of increased liver enzymes in our present series was higher than in this previous study while the frequency of grade 3 or more was less 10%. The incidence of grade or grade 3 or more adverse events was compared in those aged < 75 and ≥ 75 years under almost the same relative dose intensity without variation in starting dose by age (data not shown). In addition, the incidence of comorbidities such as hypertension, diabetes mellitus and smoking history was similar between the two groups and did not differ to that in the previous reports. Seven patients had Grade 4 adverse events; among these, six were aged < 75 years, while the patient aged ≥ 75 years experienced a non-symptomatic increase in lipase followed by improvement when sunitinib dose was decreased from 50 mg to 37.5 mg. This allowed the continuation of sunitinib until the development of progressive disease. We therefore assume that adverse events depend not only on age but also on individual characteristics or ethnicity.

Limitations of the present study include its small sample size and the bias inherent to retrospective studies. In addition, our study did not include patients with severe comorbidities and did not assure the appropriateness of stratification by age 75-years. Given the well-known difficulty in enrolling elderly patients in prospective clinical trials because of comorbidities and concerns over the toxic effects of treatment, a large scale retrospective study with high quality is warranted. Nevertheless, the present study provides additional data on the relationship between age and sunitinib treatment in patients with advanced RCC treated in a Japanese university hospital.

Conflict of interest

The authors declare that they have no conflict of interest.

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